Co-morbidity of Tuberculosis with Mood Disorder: Prevalence, Risk Factors, Incentives Effect and Tuberculosis Treatment Outcomes in Taiwan

by
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ABSTRACT

Background: Tuberculosis (TB) is a leading cause of death from an infectious disease throughout the world. The incidence rate of TB in Taiwan remains higher than that of most developed countries. Mood disorders may have an important impact on the adherence to TB treatment. Taiwan's government provided pay-for performance for TB programs (P4P) as an incentive; however, the impact of psychological factors on TB treatment is rarely recognized and studied. The aims of this study are 1) to investigate the prevalence and epidemiology of mood disorder, and examine patients' demographic characteristics and their associations among TB patients; 2) to evaluate the impact of mood disorder on TB treatment default and TB patients' mortality; and 3) to examine the impact of P4P effect on TB treatment default and TB patients' mortality.

Methods: The secondary health insurance dataset from Taiwan National Health Insurance Research Database (NHIRD) and Taiwan CDC TB Register data were used for this study. The study population consists of all newly diagnosed TB patients from 2002 to December 2007 in Taiwan. Outcome measures include mood status, TB treatment default rate and mortality. We used Chi-square and multivariate regression to analyze the relationship between mood status, risk factors, P4P effect and TB treatment default. The Cox proportional hazards regression models was used to identify factors associated with death. Kaplan–Meier method was used to evaluate mood disorder and P4P program impact on patient survival.

Results: The prevalence of mood disorder among TB patients was 26.75 % in Taiwan, this was two times higher than in the general population (12.6%). Anxiety was the

leading emotional problem (83.4%). TB patients who were elderly, females, and had higher income, disability, and high Charlson comorbidity index score (CCI) had a significantly higher chance of having a mood disorder. Risk factors for patients in the default group were having a mood disorder and being female. Regional level hospitals and family medicine specialties had the highest default rate (see glossary) Patients with mood disorders, were elderly, male, of lower income, disabled, and with high CCI had significantly higher risk of increased mortality. P4P in TB programs can decrease the default rate but had no significant influence on all-cause mortality.

Conclusions: Our findings indicated that TB patients had a higher prevalence of mood disorders than in general population. Mood disorder posed as a barrier in TB treatment adherence. TB patients with mood disorder had significantly higher mortality and lower survival rates. P4P in TB programs was an effective incentive for decreasing default but no significant influence on all-cause mortality.

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1. CHAPTER ONE: INTRODUCTION

1.1 Background

Tuberculosis (TB), a communicable disease, has been a major cause of death for thousands of years. Although there are currently many efforts to control this disease, which includes well-developed lab technology, standard treatment and a better healthcare delivery policy; TB is still a leading cause of death from infectious disease throughout the world (WHO, 2015c). Today, there is still an estimated nine million incident cases of TB globally, which is equivalent to roughly 125 cases per 100,000 population as seen in 2014. Nearly 60% of new TB cases occurred in the South-East Asia and Western Pacific Regions (WHO, 2015c). According to the report of Center of Disease Control in Taiwan (TCDC), the incidence rate of TB declined from 74.6 cases per 100,000 population in 2002 to 49.4 per 100,000 population in 2013 (TCDC, 2014c)(Table 2.1). Compared to other developed countries, the TB incidence rate in Taiwan remains 17.9 times higher than the USA's and 3.4 times higher than Japan's (the rate in the USA was about 3.8 per 100,000 population, 15 per 100,000 in the United Kingdom and 20 per 100,000 in Japan (TCDC, 2014c)(Table 2.2). A total of 1.5 million people died from TB in the year 2013 (WHO, 2015c). TB morbidity and mortality are important indicators of public hygiene. The TB death rate was 3 per 100,000 population in Taiwan, which is also higher than that of the USA and Canada (0.15 per 100,000 population in USA, 0.21 per 100,000 population in Canada)(TCDC, 2014c). This suggests that Taiwan needs to enhance management strategies to achieve the WHO's goal, which is to have a TB incidence rate less than 1 per 100,000 population by 2050 (WHO, 2014a).

Tuberculosis is widespread and affects many areas of life, including social policies.

Infectious pulmonary tuberculosis (PTB) is a very contagious disease that is transmitted by air through various airways, such as the nose and the mouth. It can lead to widespread infections if not properly controlled: 1 billion individuals may become infected, 150 million would exhibit symptoms, and 36 million may die from infection between 2002 to 2020 (WHO, 2014a). Today, the treatment procedure for TB is standardized, and patients can be cured as long as they follow medical instruction (TCDC, 2015). In fact, many researchers reveal that the failure to follow the TB treatment is mainly attributed to non-completion of treatment and noncompliance of the prescribed drug regimens. Medication non-compliance has been recognized as one of the most critical challenges in achieving successful management of this disease (Chung, Chang, & Yang, 2007; Gelmanova et al., 2007; Kruijshaar et al., 2010; Munro, 2007; Neves, Reis, & Gir, 2010; WHO, 1997). Noncompliance to medication treatment for tuberculosis is a serious issue that, if not properly dealt with, can lead to failure of the drug treatment, relapses of symptoms, and the emergence of drug resistance. It has been found that there are strains of tuberculosis that are resistant to many drugs and as such, have been thought to be associated with diminished mental health, the loss of work and social relationships, as well as feelings of hopelessness and stigma (Baghaei et al., 2011; Chang, Chiu, Chiang, Lu, & Liou, 2011; Courtwright, 2010; Gelmanova, et al., 2007; Jiang, Yen, & Wang, 2011; L. Li et al., 2009; Neves, et al., 2010; Annika Sweetland, Albújar, & Echevarria, 2002; Tulsky JP, 2004).

Mood disorder has an important effect on adherence to treatment for many health conditions such as HIV, tuberculosis, diabetes, etc (Prince M, 2007). TB is associated with psychiatric morbidity, a particularly depressive disorder that has been recognized as a cause of poor compliance as well as increased morbidity and mortality to the disease.

Despite this recognition, the amount of research that has been put into co-morbidities between tuberculosis and common mental disorders is surprisingly low. Little attention has been given to the identification of mood disorder among TB patients, particularly in Taiwan. No study yet has examined the prevalence rate of mood disorder among TB patients and evaluated its impact on TB treatment outcomes in Taiwan. The Bureau of National Health Insurance (BNHI) in Taiwan initiated the pay-for-performance (P4P) program in November 2001, which gave healthcare providers incentives to provide TB patients with more holistic care. It is anticipated that healthcare providers will provide TB patients not only with better physical care but also with psychological and social health care under this program. However, The impact of the P4P program on TB treatment outcomes for patients with both TB and mood disorder remains unknown.

1.2 Study Aims

This study aims: 1) to investigate the prevalence and epidemiology of mood disorder, and examine patients' demographic characteristics and their associations among TB patients; 2) to evaluate the impact of mood disorder on TB treatment default and TB patients' mortality; and 3) to examine the impact of P4P effect on TB treatment default and TB patients' mortality.

1.3 Significance

The results of the proposed study can provide more information for policy makers to shape a better TB control plan in Taiwan. If mood disorder among TB patients adversely affects TB treatment compliance, it may be important to encourage clinicians to pay more attention to their TB patients' mental conditions, screen TB patients for depressive symptoms, as well as refer these patients to mental health professionals, to monitor their

compliance with treatment.

2. CHAPTER TWO LITERATURE REVIEW

2.1 Tuberculosis (TB)

2.1.1 TB disease description

Tuberculosis (TB) is still prevalent worldwide today, especially in undeveloped and developing countries. TB is a chronic infectious disease caused by *Mycobacterium tuberculosis*. It is spread through the air from one person to another. The TB bacteria are dispersed into the air when a person with TB disease of the lungs or throat coughs, sneezes, speaks, or sings. These bacteria can usually stay in the air for several hours, depending on the environment. People nearby may breathe in these bacteria and become infected. Most people who are infected with *Mycobacterium tuberculosis* are initially protected by the host's immune system. People, who first initially become infected, due to their immunity, will not become sick; this occurs in about 95 percent of infected individuals and is called latent TB infection. There will be life-long re-activation and there may be a potential danger to the host. If there is an onset of a disease affecting the immune system (such as AIDS), a disease whose treatment affects the immune system (such as chemotherapy in cancer or systemic steroids in asthma, SLE, or arthritis), a disease in an older individual, or malnutrition, the immune system may be compromised and may lead to its degradation (CDC, 2012; Sutherland, 1976; WHO, 2011). This can be dangerous for an individual because a latent tuberculosis infection has the potential to develop into tuberculosis at any time.

A TB infection spreads through the blood or lymphatic system to the lungs to cause

extra-pulmonary tuberculosis (such as tuberculosis meningitis) in only 5% of those with an early TB infection. TB can occur in any organ or tissue of the body, such as the lymph nodes, meninges, pleura, kidney, bone, skin, digestive tract, or urogenital tract, but the incidence of extra-pulmonary is much lower compared to pulmonary TB.

2.1.2 Symptoms of TB

Symptoms of TB depend on the part of the body infected. The lung is the most common place where the bacteria usually grow. TB in the lungs may cause symptoms such as a bad cough that can last 3 weeks or longer, pain in the chest, the coughing up of blood or sputum (phlegm from deep inside the lungs). Other symptoms of TB are weakness or fatigue, weight loss, no appetite, chills, fever, and sweating at night. Symptoms of TB in other parts of the body depend on the area affected (Hsueh et al., 2006).

2.1.3 Screening and diagnosis of TB

Finding *Mycobacterium tuberculosis* in sputum (TB culture or smear) is the most important diagnostic evidence for the disease. Sputum of TB patients is contagious and is a key target of TB control. Chest X-rays may be used to rule out the possibility of pulmonary TB in a person who has had a positive reaction to a Mantoux tuberculin skin test (TST) or a positive TB blood test, and has no symptoms of the disease. Lesions may appear anywhere in the lungs and may differ in size, shape, density, and cavitation.

2.1.4 TB treatment

TB is treated using WHO-recommended regimens. The initial phase consists of two months of isoniazid (INH), ethambutol (EMB), rifampin (RMP) and pyrazinamide (Z), followed by a 4-month continuation phase consisting of INH, EMB and RMP (WHO,

2014b).

According to an investigation by WHO, if patients take the medicine regularly, the one-year cure rate can reach 95% or higher. The failure of TB treatment is mainly attributed to non-completion of treatment and noncompliance to the prescribed drug regimens (TCDC, 2015; WHO, 2005, 2014b). Multidrug-resistant TB (MDR-TB) is defined as TB caused by organisms resistant to at least isoniazid (INH) and rifampin (RMP). MDR-TB is difficult to treat and generally requires a minimum of 18–24 months of therapy with second-line medications that are less effective and more toxic.

2.1.5 The burden of disease caused by TB

According the report from WHO, the incidence of TB is generally greater in men than in women, greater in the elderly than in the young, and greater in the lower social classes than in the higher social classes. The prevalence of TB is low in developed countries, where most cases are intrinsic (endogenous), that is, from the old fibrosis or calcification reactivation. On the contrary, in developing and undeveloped countries, the prevalence of TB is high and is mostly due to external infection (WHO, 2011).

In the United States, there was a steady 5–6% annual decline in the case rate of TB. TB was found to be associated with HIV infection, homelessness, drug use, foreign birth and racial/ethnic minority status. Before 1986, foreign-born persons accounted for 22% of TB cases; by 1997, this had increased to 39% and in 2007 it had reached 58% (Murray et al., 2014). The TB case rate in 2011 for foreign-born persons was 12 times greater than the rate for US-born persons, and for Blacks it was 8.5 times greater than for Whites (CDC, 2012; Che & Antoine, 2009).

In Taiwan, the incidence rate of TB declined from 74.6 cases per 100,000 population

in 2002 to 49.4 per 100,000 population in 2013 (TCDC, 2014c) (Table 2.1). The mortality of TB also went down from 5.68 per 100,000 population in 2002 to 2.7 per 100,000 population in 2013. Tuberculosis control in Taiwan is still well behind TB control in developed countries. Taiwan's CDC declared on World Health Day 2005, that the number of tuberculosis patients would be halved in ten years (TCDC, 2014a). That is, incidence would drop from 16,472 new cases each year to 7500. Until 2014 the incidence of TB in Taiwan was still around 11,610. WHO had proposed a new post-2015 Global TB Strategy in May, 2014 (WHO, 2015b). The new targets are to reduce TB deaths by 95% and to decrease new cases by 90% between 2015 and 2035. Much progress is needed for prevention of TB in Taiwan.

Table 2.1 Taiwan TB Incidence and Mortality Rate, 2002 – 2013

Year	Case	Incidence	Death	Mortality
2002	16,758	74.6	1,277	5.68
2003	15,042	66.67	1,309	5.8
2004	16,784	74.1	957	4.23
2005	16,472	72.5	970	4.3
2006	15,378	67.4	832	3.6
2007	14,480	63.2	783	3.4
2008	14,265	62.0	762	3.3
2009	13,336	57.8	748	3.2
2010	13,237	57.2	645	2.8
2011	12,634	54.5	638	2.8
2012	12,338	53.0	626	2.7
2013	11,528	49.4	621	2.7
Incidence and mortality shown as per 100,000 populations				

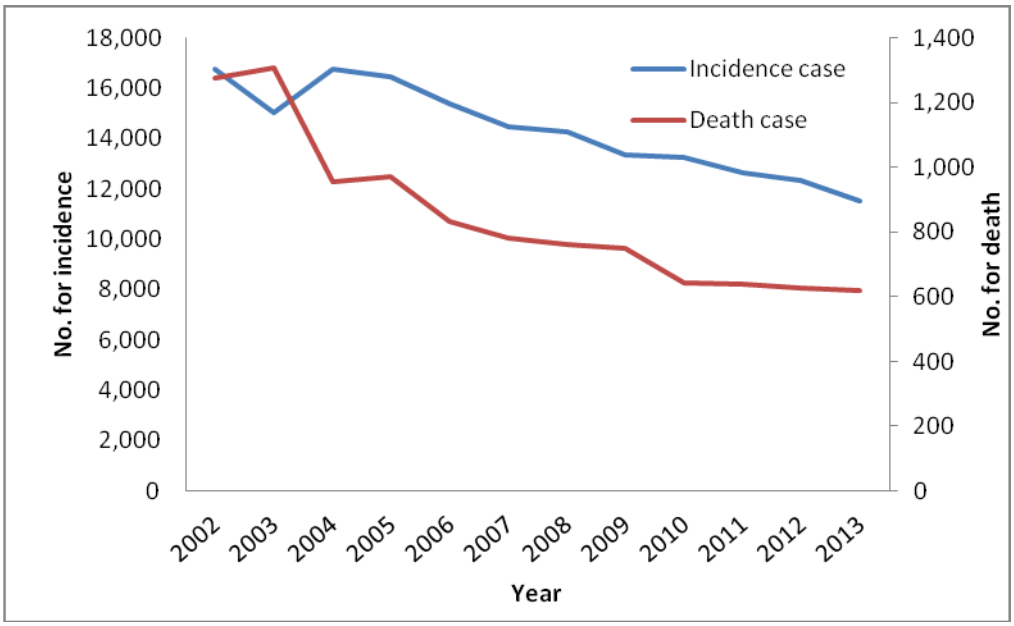


Figure 2.1 Taiwan TB Incidence and Mortality Rate, 2005 – 2013

The demographic characteristics of the TB cases were described as following (TCDC, 2014c):

1. By gender: The male to female ratio was 2.3 : 1.

2. By age: Most cases fell in the age group of ≧65 years which accounted for 52.1% of total cases. Incidence increased with age. The lowest incidence occurred among the 0-14 years of age group.

3. By month (based on notification date): cases were spread out throughout the year; no epidemic season was found.

4. By region: Cases occurred more frequently in the metropolitan area such as Taipei, Taichung and Kaohsiung city than in rural areas, and more in the South than in the North (Figure 2.2).

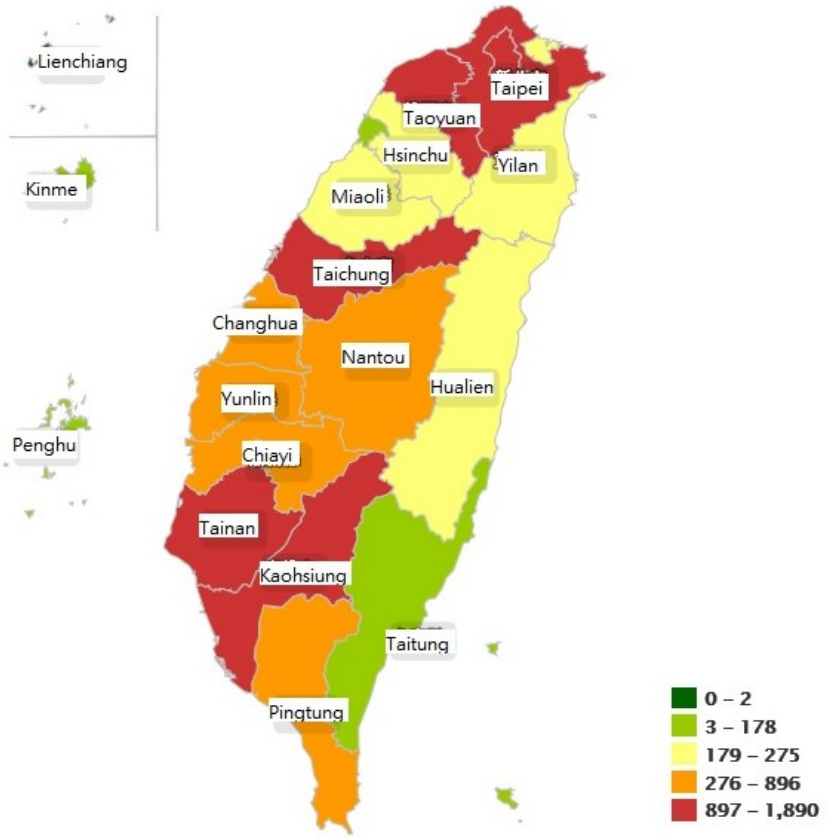


Figure 2.2 Geographic distribution of TB patients in Taiwan (2003-2015)

TB patients' mortality in Taiwan in 2013(TCDC, 2014b):

1. By gender: There were 479 deaths among males and 147 deaths among females. The male to female death ratio was 3.26: 1. The male mortality rate was 4.1 cases per 100,000 population and the female mortality rate was 1.3 cases per 100,000.

2. By age group: The tuberculosis mortality rate increased with age. Of the 621 tuberculosis deaths in 2013, 83% (519/621) were of elderly individuals aged 65 years and over.

3. By area: The tuberculosis mortality rate was the highest in Taitung County with a rate of 9.2 cases per 100,000 population, followed by Hualien County (6.8 cases per 100,000 population), and then Kinmen County (6.3 cases per 100,000 population), according to the Surveillance Reports of Selected Diseases. The overall distribution of deaths by tuberculosis in 2013 exhibited a pattern of a higher mortality rate in the east and south and a lower rate in the north (TCDC, 2014c).

In recent years, transportation has become more convenient. People have greater chances of interacting with each other. TB has become easier to transmit. From table 2.2, we may compare the burden of TB in Taiwan with major developed countries and other adjacent Asian countries such as mainland China, Philippines, Indonesia and India. The TB incidence and prevalence rate in the Southeast Asian countries are obviously higher than Taiwan and most developed countries. Raising awareness and building an international interchange network is important in order to protect people from TB.

Table 2.2 Estimated TB burden by countries, 2011 (TCDC, 2014c)

Estimated TB burden, by countries, 2011

	Popu-lation (Millions)	Incidence [a]		Prevalence		Mortality	
		Number (thousands)	per 100 000 pop per year	Number (thousands)	per 100 000 pop per year	Number (thousands)	per 100 000 pop per year
Taiwan	23	15.9	68	20.6	89	0.638	3
United State of America	315	12	3.8	16	5	0.47	0.15
Canada	34	1.6	4.8	2.2	6.3	0.071	0.21
Japan	127	25	20	35	28	2.3	1.8
South Korea	49	53	109	72	149	2.7	5.6
Hong Kong	7	5.4	77	7.3	103	0.19	2.6
Singapore	5	1.9	36	2.3	44	0.087	1.7
Malaysia	29	23	81	31	107	1.6	5.4
Philippines	95	260	270	460	484	24	26
China	1,368	1,000	75	1,400	104	48	3.5
Australia	23	1.4	6.3	1.9	8.2	0.04	0.18
Thailand	67	82	124	110	168	9.5	14
Indonesia	244	460	187	730	301	67	27
India	1,221	2,200	181	3,000	249	300	24
Viet Nam	90	140	151	200	227	19	21
United Kingdom	62	9.5	15	13	20	0.34	0.54
Russian Federation	143	140	97	190	135	21	15
Global	6,972	8,700	125	12,000	176	980	14
AFR	870	2,300	262	2,700	310	230	26
AMR	951	280	30	400	42	19	2
EMR	605	660	109	1,100	182	100	17
EUR	902	400	44	580	64	40	4.5
SEAR	1,812	3,500	191	5,000	278	480	26
WPR	1,833	1,600	90	2,500	134	110	6.1

Note: [a] All estimates includes TB/HIV co-infected cases.

[b] International county profiles quotes from the WHO Global Tuberculosis Report 2013.

2.2 Tuberculosis with Mood Disorder

2.2.1 Mood Disorder

Mood disorder is a symptom that can be used to anticipate the beginning, as well as the advancement, of physical and relational disabilities. On the other hand, a disability can be an indicator for depression in older adults (Bruce, Seeman, Merrill, & Blazer, 1994; Cole & Dendukuri, 2003; Holwerda et al., 2007). Several studies show the biological effects of depression on the human body. The effect on serotonin metabolism changes cardiac function, platelet aggregation, and vasoconstriction (McCaffery et al., 2006). Additionally, depression effects cortisol metabolism by increasing cortisol production, which leads to inflammation. It also affects cell-mediated immunity that impairs T-cell mediated function, where a reduced natural-killer cell count increases vulnerability to infectious diseases (Zorrilla et al., 2001). Furthermore, many diseases create a psychological burden due to lifestyle changes, unpleasant side effects from therapeutic regimens, feelings of stigma, pain, the loss of social support, the breaking down of key relationships, having a life-threatening disease, and difficulty of living with the illness (Bratek, Zawada, Barczyk, Sozanska, & Krysta, 2013). This psychological burden may trigger mood disorder in an individual, delay help-seeking, cause them to withdraw from treatment, and perhaps even worsen the prognosis.

2.2.2 Tuberculosis and Mood Disorder

In 2007, Lancet had a series of articles related to mental health and disease. These articles showed that mental disorders increase the risk for communicable and non-communicable diseases. Conversely, many health conditions increase the risk for mental

disorder, and co-morbidity complicates help-seeking, diagnosis, treatment, and influences prognosis (Andrews & Titov, 2007; Prince M, 2007). According to a WHO report in 2005, neuropsychiatric conditions accounted for 31.7% of all years-lived-with-disability (WHO, 2005). Depression is the major contributor to this disability (unipolar depression, 11.8%, and bipolar depression, 2.4%). A WHO World Health Survey in 2007 studied 245,404 adults aged 18 years and older from 60 countries in all regions of the world. This survey showed that compared with other chronic diseases such as angina, arthritis, asthma, and diabetes, mood disorder produced the greatest decrement in healing (Moussavi et al., 2007).

In recent years, the pharmacological treatment of TB has been well established. The standard anti-TB therapy consists of four medications and takes at least six to nine months to complete. Most TB patients need to tolerate serious risks of adverse reactions such as skin rashes, pruritus, hepatitis, nausea/vomiting, thrombocytopenia, influenza-like illness, arthralgia and neuropsychiatric symptoms (Marra et al., 2007). Hence, it is crucial to help patients adhere to drug regimens to reduce the risk of resistance. However, compliance to treatment is sometimes difficult among patients, particularly those with co-morbid psychiatric disorders. Patients with personality disorders may not recognize the necessity of treatment for their well-being. Residential treatment and isolation are sometimes used for TB-positive psychiatric patients to limit the spread of the disease. While these practices may increase compliance, they may induce further emotional stress.

In the United States, some communities of TB patients are perceived as a source of infection and the resulting social rejection and isolation leads to long-term impairment in patients' psychosocial well-being. Many TB patients also report experiencing negative

emotions, such as depression, anxiety and fear (Kelly, 1999). According to Rubel's and Garro's study among Mexican immigrants in 1992, Ailinger's and Dear's survey in Latino immigrants in 1997, and Carey and colleagues' findings in a Vietnamese refuge in New York State, nearly all respondents had concerns that a tuberculosis diagnosis would lead to termination from their jobs and avoidance by their family and friends. Patients responded to these attitudes by isolating themselves and becoming secretive about their illness (Ailinger & Dear, 1998; Carey et al., 1997; Rubel & Garro, 1992). The psychosocial impairment experienced by TB patients may be a reflection of socio-demographic status (e.g., age, gender, and socio-economic status) and other underlying co-morbid conditions, besides TB and its treatment (Caracta, 2003; Nyamathi, Berg, Jones, & Leake, 2005; Uplekar et al., 2001). A few studies explored the relationship between socio-demographic features, clinical factors, and psychosocial well-being in TB patients. In general, the findings were consistent, but some discrepancies existed. Yang et. al. and Nyamatihi et. al. observed that females were more likely to report poorer health than males, especially regarding mental health problems, such as depression and anxiety (Nyamathi, et al., 2005; L. Yang, Wu, Guo, & Liu, 2003). Guo et. al. found that older individuals tended to have a poorer health-related quality of life than younger individuals. However, Duyan et. al. did not find significant associations between gender, age and quality of life in TB patients (Duyan, Kurt, Aktas, Duyan, & Kulkul, 2005; Guo et al., 2008). Instead, they found that better health-related quality of life was correlated with higher income, higher education, better housing conditions, better social security, and closer relationships with family and friends.

Although a few studies have conducted research related to depression and several

other diseases, such as diabetes, cardiovascular disease, COPD and HIV, there is little research on the relationship between mood disorder and tuberculosis. Estimates of the prevalence of mood disorder in patients with TB vary widely. There have been few available studies regarding the prevalence of co-morbid TB and mood disorder in MEDLINE research. Their findings are summarized in Table 2.3.

Table 2.3 Prevalence of Mood disorder among TB patients

Studies	Screening Tools	Prevalence of Mood disorder , %	Source of Patients	Mean Age, yr	Male/Female Gender, No
Aydin & Ulusahin, 2001	Composite International Diagnostic Interview (CIDI)	19% for RDtb, 21.6% for Dtb, 25.6% for MDRtb	Turkey, inpatient	20–66yr	119 male
Vega et al., 2004	Clinical criteria based on DSM-IV	52.2% for MDRtb ; 13.3% after anti-TB, and psychiatric drug therapy	Peru outpatient	26.8yr (11.8-65.1)	75 37 (49.3%) male 38 (50.7%) female
Aamir & Aisha, 2010	Hospital Anxiety and Depression Scale (HADS)	72% for RDtb 22% for MDRtb	Pakistan, outpatient	36yr	65
Mohammed O Husain, 2008	the Hospital Anxiety and Depression scale (HADS) and the Illness Perception Questionnaire (IPQ).	50 (46.3%) depressed 51 (47.2%) anxiety Negative illness perceptions were related to mood symptoms	Pakistan, outpatient	37.3yr	108 86 (79.6%) females
Rajeswari, 2005	SF36	depression (male 7%, female 10%) suicidal thoughts (male 9%, female 9%)	India outpatient	15-45yr	610 404(54%) male 206(57%) female
Kruijshaar, et al., 2010	The Center for Epidemiologic Studies Depression Scale (CES-D)	at diagnosis (high) anxiety scores 48 depression scores 22 at follow-up	UK outpatient	15-45 yr (72%)	68 29 male 34 female 5 unknown
Pan, Zhao, & Yang, 2006	Hospital Anxiety and Depression Scale (HADS)	56.1% anxiety, 2l.1%depression After psychotherapy, 5.7%anxiety, 4.1%depression	China outpatient	23±16yr 17-93yr	115 males 15 females

RDtb= recently diagnosed TB; Dtb= defaulted TB; MDRtb= multidrug resistant tuberculosis; DSM-IV

Most of these studies used the Hospital Anxiety and Depression Scale (HADS) as a screening tool for depression. The majority of the studies were conducted in developing countries (Aamir & Aisha, 2010; Aydin & Ulusahin, 2001; Mohammed O Husain, 2008; Pan, Zhao, & Yang, 2006; Rajeswari, 2005; Vega et al., 2004). In the UK study, a large proportion of the participants with TB were not born in the UK, most were Indian, Pakistani, or Bangladeshi (33%) and Black African (28%) (Kruijshaar, et al., 2010). Only one study was made up of Chinese individuals; but it had a small sample size and did not comprehensively cover the whole country. In regard to gender distribution, there were more males than females. Most females were from lower socioeconomic levels, and were illiterate. The average age of the individuals in these studies was less than 45 years old. The prevalence of depression in patients with TB was high upon diagnosis of tuberculosis, but declined after patients were recruited into psychotherapy, joined a support group, or went on drug therapy. In the UK study, higher rates of depression and anxiety were observed in the TB patients that did not comply to treatment, as well as those with more negative health beliefs. Therefore, when patients perceived a greater risk of TB, mood symptoms became more apparent. In general, the prevalence of mood disorder and anxiety is higher in those with tuberculosis than in the general population. The incidence of depression, anxiety, and psychosis emerging during the course of treatment for tuberculosis is also higher in affected individuals than in the general population. Mood disorder and lack of perceived control were independently associated with poor adherence. Treating psychological problems in patients with tuberculosis may substantially improve treatment adherence. It is noticed that Isoniazid (H), a commonly used anti-TB drug, had been reported to possibly lead to mental

syndromes and suicidal thoughts (Djibo & Lawan, 2001; Herrag, Sajiai, & Yazidi, 2011; Iannaccone, Sue, & Avner, 2002; Pallone, Goldman, & Fuller, 1993; Shah, 2009). For these reasons, it is crucial to pay more attention to the psychological status of TB patients.

In Taiwan, no study has examined the prevalence of mood disorder among TB patients, particularly patient characteristics that may be different from those in other countries. According to the report from the Taiwan CDC, male TB patients are more susceptible to TB than females; and most of those infected are elderly. In Taiwan, there is minimal disparity in the living standard, and the illiteracy rate is very low. However, even though the government has devoted many resources and manpower, such as pay-for performance and case management, to eradicate TB, it is still unknown how mental factors play a role with the disease in Taiwan's population.

2.3 Health delivery system and TB

2.3.1 Pay-for-performance (P4P) and TB

Payment systems work as different incentives to the various medical service providers; they affect medical outcomes, doctor-patient relationships, and patients' rights. Traditional payment systems can be broadly divided into: fee for service, case payment, capitation payment, total payment system (global budget), per diem, and salary (Lagarde M., 2010). While each of these systems has their advantages and disadvantages, many existing reimbursement plans do not reward high quality health care. For example, under the Diagnoses Related Groups (DRGs) system or global budget, hospitals tend to reduce the inputs into the treatment process or expenses because they are compensated by a fixed amount determined by each patient's diagnosis or by a fixed quota, rather than the

marginal cost incurred during the treatment. These traditional payment designs can result in problems of overuse, underuse, and low productivity.

Reports from the Institute of Medicine on issues concerning quality of health care have led to research on payment reform and implementation of the P4P scheme. The pay-by-quality payment method was established based on disease management. P4P is a modification of the traditional payment scheme and is based on rewarding health care providers for the quality of their care with financial or other non-financial incentives (Hackbarth, 2008; Mabotuwana et al., 2010; Mullen, Frank, & Rosenthal, 2010; Rosenthal, 2008; Vamos et al., 2011; Witter, Fretheim, Kessy, & Lindahl, 2012). The theoretical basis for designing an incentive mechanism within a payment scheme originated from the agent theory, which posits that incentive contracting occurs when an individual or organization induces and rewards another individual or organization for specific behaviors (Lindenauer et al., 2007). The concept of P4P brings both continuous and better healthcare, as well as case management into the medical care services. Case management is usually composed mainly of nurses, physicians, and public health workers or social workers (Hsieh et al., 2008). These individuals are in charge of handling the condition and treatment of the infected person through the treatment process, patient education, medication side effect evaluation, compliance assessments and anything else the physician may require. The objective behind the case managements were launched in TB control to incur better treatment outcomes as well as improve quality of life for the patients.

Hence, the performance based incentives influence provider behavior at both the individual health worker and the institution level. At the individual level, incentives are

aimed at improving the quality of diagnosis, expanding access to treatment by promoting outreach, reducing default rates, and encouraging completion of treatment. Performance based incentives aimed at the team or institution level are oriented towards improving team work and stimulating system changes to improve outcomes. Payment is usually based on a clearly defined process or outcome measures, such as: case detection, suspect referral, completion of treatment, or cured patient.

2.3.2 Healthcare providers for TB in Taiwan

In 1995, Taiwan implemented a compulsory universal health insurance program to provide universal health insurance coverage to all of its citizens. Implementation of this program involved extensive and comprehensive changes for all healthcare delivery systems, including the TB control system (Cheng & Chiang, 1997). The formerly centralized, government-budgeted, and vertically structured health system was reformed into a liberalized system with fragmented organization and distributed responsibility for TB control. The official TB control institutes were nearly all abolished and only one of the chest-specialized institutes located in Southern Taiwan remains. This universal health insurance program maintains a contract with more than 90% of Taiwan's health care institutions and works without a referral system; insured patients are completely free to choose their physician or hospital. Thus, all patients with TB can freely seek medical aid at any healthcare institution from offices of primary practitioners to hospitals. Since that time, TB cases have been identified and treated in general care facilities.

The registration for TB patients started from 1957. It was aimed at sputum positive infectious tuberculosis patients. Thereafter, the target was expanded. Starting in 1991,

all active tuberculosis patients were to be notified and registered. However, the process of notification in medical centers was not performed smoothly enough to accurately reflect epidemic situation. The Bureau of National Health Insurance enforced the policy of "No Notification, No Payment" for TB in July 1997. In 2001, CDC has set up the TB Division to handle the notification of TB Death Data for matching and notification through the Internet (suspected cases were also included). Consequently, different methods of notification produced different notification rates. As a result, the number of TB patients notified by medical centers rose rapidly. The epidemic statistic data notification rate has come closer to the true epidemic situation.

Many studies have shown the association between hospital level and ownership information and TB-related policies and outcome performances (Hu, 2005; Tsai et al., 2010; Yu-Wei Hsieh, 2011; Yun-Hsiang Chan, 2011). Hospital level and ownership are important considerations in the empirical study of the health economy and medical management. The different hospital levels represent different service functions, task and development objectives, and also reflect the information of the number of beds (hospital size) and hospital accreditation results (i.e. quality of care). In general, the higher the rank of the hospital in regards to the hospital's medical resources, the better the quality of healthcare. The different ownership of the medical institutions represents different tax burdens for the facility (ex. public medical institutions can be exempted from business tax, income tax, house tax, etc.) and different operational objectives and management style (ex. the financial allocation of public and private hospitals). In Taiwan medical institutions are classified into four major accreditation levels: academic medical center, regional hospital, district hospital, or clinic. The accreditation criteria include

infrastructure, capacity, manpower, volume, management and administrative processes. The NHI as a single payer who reimburses providers by provider accreditation level, quality of care or provider level. The academic medical centers tend to get the highest fee and clinics tend to get the lowest fee for most services. More than 90% of the hospitals are private, not-for-profit; and, approximately 97% of the clinics are privately owned. Taiwan has a closed hospital system, most hospital physicians are under contract and have their salaries paid by the hospital. Our study will use these variables to evaluate the influence of health care providers on mood disorder TB patients.

2.3.3 P4P on Tuberculosis in Taiwan

In recent years, Taiwan's National Health Insurance program implemented a quality payment system for the treatment of breast cancer, tuberculosis, diabetes, asthma, and hypertension. In order to make TB treatment more effective and avoid rapid spread of the disease, the Bureau of National Health Insurance (BNHI) in Taiwan started the implementation of a P4P payment demonstration project for the treatment of TB in central Taiwan in October, 2001. By January of 2004, P4P became a national program. According to the report from the CDC, there had been a total of 250 hospitals in Taiwan participating in the pay-for-performance program for TB by June, 2006; and, about 70% of TB patients were covered by this program. The P4P program for TB treatment aimed to improve patient treatment compliance to increase the TB treatment success rate and reduce the financial burden of the NHI from TB patients in Taiwan. Hospitals in Taiwan could choose to join the P4P plan if they met the following criteria: (1) if hospitals choose to join P4P for TB, they should have a health insurance contract with the BNHI; (2) hospitals should be approved by the CDC of Taiwan; (3) physicians in the

participated hospital must have specialist licenses on infectious disease, tuberculosis, chest medicine or have had related training or certification; (4) if the hospital has more than 100 new cases in one year, the hospital must hire a full time TB case manager.

The P4P program is a TB treatment plan that is broken up into 4 phases; each phases lasts for 3 months. In the P4P for TB plan, health care providers can get a bonus if they can accomplish the care task in each phase without interruptions or drop out. The most typical conditions of putting into action the P4P to control diseases is the reward health care providers can earn. The rewards vary by stage of the P4P program, please see the appendix A

2.3.4 Mood Disorder and P4P on Tuberculosis in Taiwan

Previous literature suggests that mental distress is very common in TB patients. However, there are rarely psychological professionals involved in a TB case management team or P4P care program. When we look up a “TB management record card”, there are no psychological observational records. Also, on the official “national surveillance network of communicable disease” follow up system, there is no mental condition record. Although using the psychological screening tool to evaluate TB patients has rarely been done, it can be seen that the impact of mood disorder among TB patients has been neglected.

A few studies have found that the outcome of P4P on TB cases in Taiwan has been beneficial. In Hsieh’s study, the P4P program improved the treatment success rate by approximately 13% on average and it was most effective at the lowest leveled hospital (Hsieh, et al., 2008). Tsai also found that the default rate declined after "P4P on TB"

implementation (Tsai, et al., 2010). The study by Li showed that both the cure rate and average length of treatment for cured cases improved after the implementation of the P4P for TB in Taiwan (Y. H. Li et al., 2010). Hospitals using case management with DOTS were able to improve adherence to medication by tuberculosis patients (Hsieh, et al., 2008). Although a few studies have discussed the effectiveness of the P4P policy, no quantitative study yet discussed the major mental impact of TB on patients. It is believed that since physicians and hospitals gain financial incentives from the P4P program, they should be providing TB patients not only with physical care but also psychological and social healthcare as well. However, the current goal of TB management is to achieve a microbiological "cure" and there has been little effort taken to consider patients' psychosocial well-being. Therefore, there is a need to explore whether the P4P policy will mend the impact of mood disorder in TB patients.

3. CHAPTER THREE MATERIALS AND METHODS

3.1 Conceptual Framework

I adopted Donabedian's structure-process-outcome model (see Figure 3.1) (Donabedian, 1966) for the conceptual framework of this study (see Figure 3.2). This model is widely used in studies regarding the quality of care provided to patients. It models the quality of care as a three-dimension categorization that includes structure, process, and outcome. The structure aspect indicates the hospital characteristics that influence the health care provided, such as human, physical, and financial resources. Process refers to the actual care-related services that are given by health providers to patients. The process of the care provided is not only determined by health care providers but also by patients and their families. The process aspect of care is also influenced by the structure variables. Outcome is defined as "*changes (desirable or undesirable) in individuals and populations that can be attributed to healthcare*." It can be affected by both structure and process. In the proposed study, I modified Donabedian's structure-process-outcome model to fit the traits for TB care and treatment. I also included patient characteristics as they are important indicators for TB outcomes and the process of care. Please see below for the conceptual framework developed for this study.

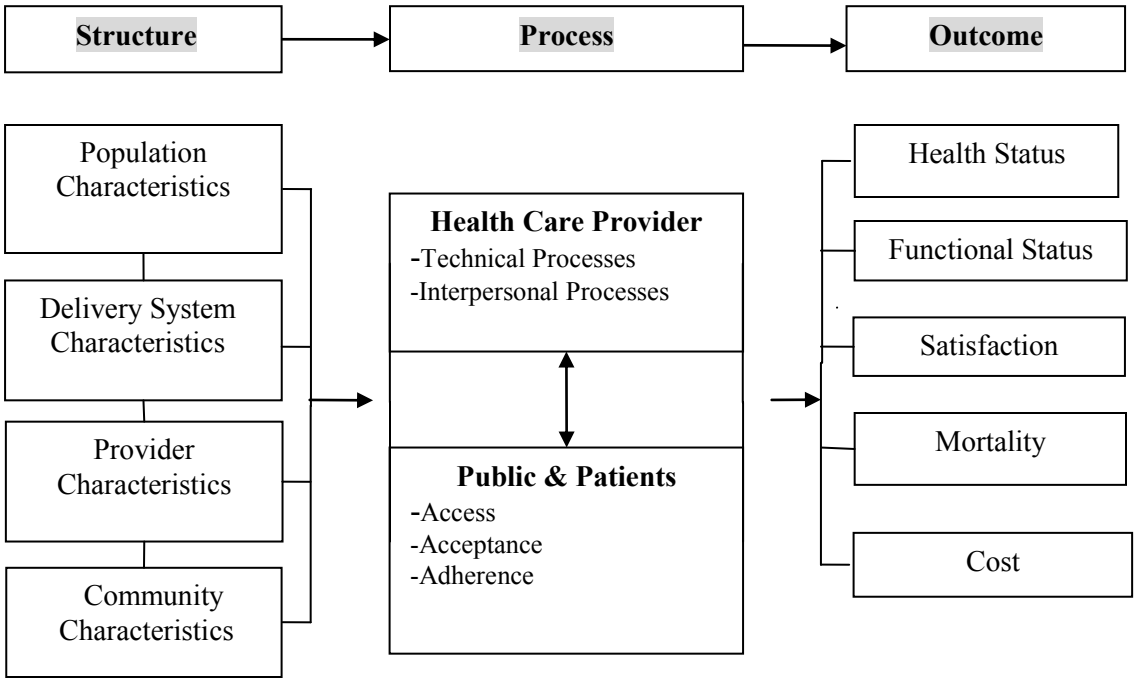


Figure 3.1 Dimensions of quality of healthcare. Adapted from Donabedian

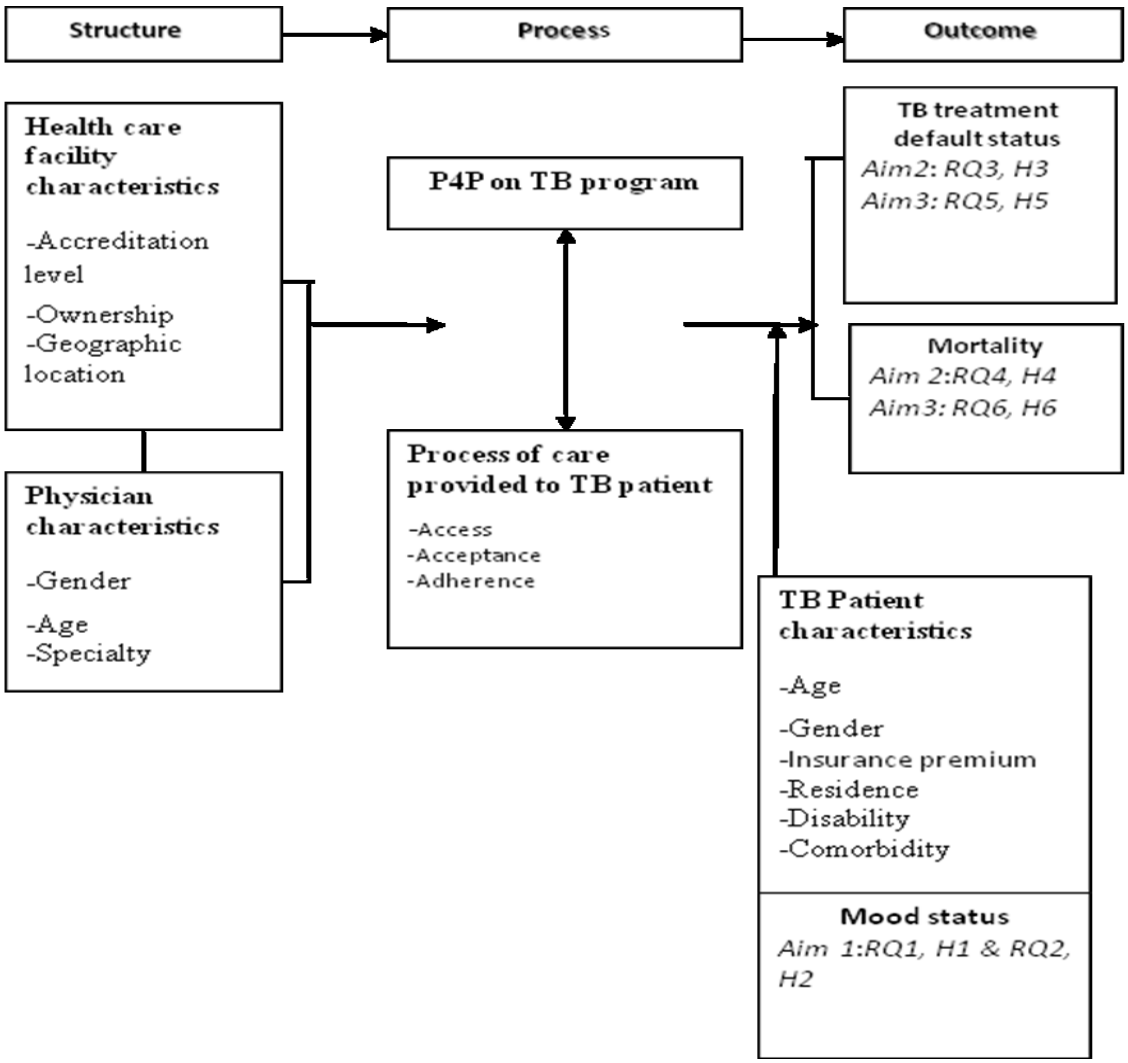


Figure 3.2 Conceptual Framework for the Study

3.2 Research Questions and Hypotheses:

To achieve the research **aim 1**) to investigate the prevalence and epidemiology of mood disorder, and examine patients' demographic characteristics and their relationship among TB patients in Taiwan, the research questions and hypotheses are:

Research question 1: What is the prevalence of mood disorder among TB patients in Taiwan?

Hypothesis 1: The prevalence of mood disorder is higher in TB patients than in the general population in Taiwan.

Research question 2: Among TB patients, what patients' characteristics are associated with the presence of mood disorder in Taiwan?

Hypothesis 2: Patient's age, gender, socio-economic status, location of residence, disability and other co-morbidities are associated with the presence of mood disorder among TB patients.

To achieve the research **aim 2**) to evaluate the impact of mood disorder on TB treatment default and TB patients' mortality, the research questions and hypotheses are:

Research question 3: Do TB patients with mood disorder have the same rate of treatment default rate as TB patients without mood disorder in Taiwan?

Hypothesis 3: TB patients with mood disorder have a higher default rate than TB patients without mood disorder in Taiwan.

Research question 4: Do TB patients with mood disorder have the same mortality as TB patients without mood disorder in Taiwan?

Hypothesis 4: TB patients with mood disorder have a higher mortality rate than TB patients without mood disorder in Taiwan.

To achieve the research **aim 3**) to examine the impact of mood disorder and P4P effect on TB patients' mortality, the research questions and hypotheses are:

Research question 5: Does P4P with the TB program improve TB treatment default rate among TB with mood disorder patients ?

Hypothesis 5: TB patients with mood disorder enrolled in the P4P program have a higher default rate than those patients who are not enrolled in the P4P program in Taiwan.

Research question 6: Does P4P with TB program improve mortality among TB with mood disorder patients**.**

Hypothesis 6: TB patients with mood disorder enrolled in the P4P program will have a lower mortality rate than those patients who are not enrolled in the P4P program in Taiwan.

3.3 Research Methods and Design

3.3.1 Study Design

Using the national data sets from the Bureau of National Health Insurance and the Taiwan Center for Disease Control and Prevention (TCDC), this study enrolled the newly developed TB cases from the years 2002 to 2007 and observed their TB therapy and outcome until 2010 in Taiwan to describe the epidemiology of TB and mood disorder co-morbidities and to evaluate the impact of P4P on TB program.

3.3.2 Data Sources

National Health Insurance Research Database (NHIRD)

Taiwan developed a unique health insurance system based on a single-payer government run National Health Insurance (NHI) Program in March 1995. By 2010, the

NHI provided coverage for more than 99% of Taiwan's population (23.74 million people). The National Health Insurance Research Dataset (NHIRD) is managed by the Bureau of National Health Insurance (BNHI). The dataset contains original claim data for all of the reimbursed healthcare services. We retrieved data from the NHIRD (Longitudinal Health Insurance Database 2000; LHID 2000) from 1,000,000 randomly sampled persons who had enrolled in 2000. All of the data for enrollees from 2000 to 2010 were de-identified and further scrambled by the National Health Research Institutes in Taiwan before release. It includes historical claims data for 1 million subjects randomly selected from the 23.74 million individuals insured by the NHI program. In this study, I use the data file for the ambulatory services and in-patient to identify patients with TB and mood disorder using the diagnosis codes. The data file provides patient characteristics, including gender, age, insurance premium, location of residence, status of disability and co-morbidity. The data file also indicates which health care facility the patient visits and which physician the patient sees. The facility ID and healthcare provider ID in the ambulatory service data file will allow me to link the file to the facility data file and the medical personnel data file, where I can obtain facility characteristics (e.g., level, ownership, location) and physician characteristics (e.g., gender, age, specialty). Please see the table at the end of this section for each of the NHIRD data files and the variables they provide for this study. Table 3.1 shows the variables used for this study and their definitions.

Registry for Tuberculosis Patients

The TCDC manages a registry for all TB patients. Registration for TB patients started in 1957, and the computerized National TB Register with a registration network was established in 1994. Information on TB patients is reported to the TCDC by health

care institutions. The data set provides some of the treatment outcomes for each TB patient, including TB treatment default and death. Following definitions from WHO, a negative sputum smear in the last month of treatment, being identified as cured on at least one previous occasion, or having completed treatment are detection methods for TB patients.

Table 3.1 Variables Used for the Study and Definitions

NHIRD data files	Description and Variables
Registry for contracted medical facilities (HOSB)	This file contains information on all health care facilities contracted with BNHI and can be linked to the TB patients' ambulatory services claim data. It provides the following variables for this study: ✓ Facility ID ✓ Ownership ✓ Accreditation level ✓ Geographical location
Registry for medical personnel (PER)	The PER file consists of information for medical personnel who work for the contracted health care facilities. The following variables are available from this file: ✓ Medical personnel ID ✓ Physician gender ✓ Physician birthday (used to calculate age) ✓ Physician specialty
Registry for beneficiaries (ID)	This file contains information for BNHI beneficiaries. It provides the following variables for the study: ✓ Beneficiary ID ✓ Birthday (used to calculate age) ✓ Gender ✓ Insurance premium (a proxy for beneficiary's socio-economic status) ✓ Beneficiary's work or residence location ✓ Death
Ambulatory care expenditures by visits (CD)	This file contains information about a patient's outpatient visits. The following variables will be used for the proposed study from the file: ✓ Beneficiary ID ✓ Facility ID ✓ Medical personnel ID ✓ Date of the visit ✓ Diagnosis (ICD-9-CM, used to identify mood disorder and other co-morbid) ✓ Disability
TCDC TB Register data files	**Description and Variables**
Registry for TB patients	This file contains information about a patient's treatment outcome. The following variables will be used for the proposed study from the file: ✓ Anti-TB medication start and end date, ✓ Treatment interrupt date

3.3.3 Study Population

Study Subjects

P4P on TB programs in Taiwan was implemented on November 2001 and ended at the end of 2007. Study subjects consist of newly developed TB cases from 2002 to December 2007. Cases with ICD-9-CM code 010–018 were included in this program, but multi-drug resistant tuberculosis (MDR-TB) cases, extra-pulmonary TB cases and atypical mycobacterium tuberculosis cases were excluded.

3.3.4 Measures and Variables

Dependent and Independent Variables:

Default status

According to the TCDC's and US CDC's definitions, default status represents whether a TB patient's treatment is interrupted for two months or longer. This variable is defined as a patient with a duration between two visits that is longer than two months or a patient who stops going to the TB medical visit before he/she completes the treatment. This variable is a binary variable, coded as 1 for either situation mentioned above, and coded as 0 if otherwise.

Mortality

The variable comes from the record of NHIRD. We follow up enrolled patients from year 2002 to the end of 2010. Mortality is coded by 1 if a patient dies, and 0 otherwise.

Main Independent Variables

Mood status

A patient with mood disorder and anxiety was identified by using the ICD-9-CM code in the ambulatory and inpatient services claim file. If a patient had one or more outpatient visits or hospitalizations before TB is identified, or during the TB treatment period with the following ICD-9-CM code, he/she was identified as a patient with mood disorder and anxiety: bipolar: 296.0X–296.1X, 296.4X–296.8X; depressive disorder: 296.2X–296.3X, 300.4, 311.X; anxiety: 300–300.3, 300.5, 300.7–300.9; or adjustment reaction: 309. Mood status is a dichotomous variable with 1 denoting the identification of mood disorder and 0 denoting no mood disorder. Table 3.2 shows the definitions of mood disorder.

Table 3.2 Definitions of Mood Disorder

Disease	ICD-9-CM† Rubrics
Bipolar disorder	296.0, 296.1, 296.2, 296.3, 296.4, 296.5, 296.6, 296.8, 296.9
Depressive disorder	296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26 296.3, 300.4, 311
Anxiety	300.1, 300.2, 300.3, 300.5, 300.7, 300.8, 300.9
Adjustment reaction	309

† ICD-9-CM indicates International Classification of Diseases, Ninth Revision, Clinical Modification.

Pay-for-Performance (P4P)

The program was officially named "Pay-for-Performance on Tuberculosis" (P4P on TB). Hospitals in Taiwan could choose to participate in the P4P on TB program if they satisfied the eligibility criteria. This program operated from November 2001 to the end of 2007.

Other covariates

Patients characteristics covariates:

Gender

Gender is a categorical variable with 1 indicating a male patient and 2 indicating a female patient.

Age

Age is a numerical variable, calculated as the difference between the date TB is identified and the study subject's birthday.

Urbanization

Urbanization is a categorical variable. The urbanization level was categorized using information relating to population density of the residential area, population ratio of the elderly, agriculture workers, different educational levels, and the number of physicians per 100,000 people (Liu CY, 2006). We assumed that patients lived near the medical organizations they visited most frequently. Urbanization was classified into high and low categories.

Disability

The government of Taiwan provides a premium subsidy to individuals with physical disabilities as a part of the welfare program. Therefore, we can identify an

individual's physical disability status from the NHI enrollment file. Disability is defined as a binary variable.

Insurance premium

This is a numeric variable, which is a proxy for the beneficiary's socio-economic status since the premium is based on income (presented in new Taiwan dollars). Insurance premium are divided to three categories NTD < 15,000, NTD 15,000-19,999 and ≧NTD 20,000.

Charlson comorbidity index score

This variable was defined as the number of other medical diseases identified from outpatient and inpatient claim data files. Comorbidities were selected according to the Charlson Comorbidity Index (CCI), which is the most common medical comorbidity measure to assess medical comorbidity (Charlson, Pompei, Ales, & MacKenzie, 1987; Pirraglia, Biswas, Kilbourne, Fenn, & Bauer, 2009). These comorbidities represent the chronic medical condition of the patients. Levels of comorbidity are defined using a numerical label and weights of diseases: zero, 1, 2, 3 or greater than 3 diseases.

Related risk co-morbidities

This variable investigates comorbidities that may be associated with mood disorder, which include the following: hypertension (ICD-9 codes 401–405), diabetes (ICD-9 code 250), hyperlipidemia (ICD-9 code 272), chronic kidney disease (CKD) (ICD-9 code 585), chronic liver disease and cirrhosis (CLD) (ICD-9 code 571), human immunodeficiency virus (HIV) disease (ICD-9 code 042) and schizophrenic disorders (ICD-9 code 295).

Hospital and physician characteristics covariates:

Location of a health care facility

This is a categorical variable that represents the location of health care facilities caring for TB patients. This variable is used to adjust for differences in medical resources, practice patterns, and medical environments that may confound the association between independent variables and outcome variables in the analysis. The classification of this variable adopts the six branches identified by the BNHI, including the Taipei branch, Northern branch, Taichung branch, Southern branch, Kao-Pin branch, and Eastern branch.

Accreditation level of a health care facility

This is a categorical variable which represents the contract category of the healthcare facility with the BNHI. The accreditation level of a healthcare facility is determined by a panel of experts during an on-site inspection of hospital size, capability, and quality of healthcare services. Accreditation for health facilities is divided into four categories, including medical centers, regional hospitals, district hospitals, and others (e.g., clinics).

Ownership of a health care facility

This is a categorical variable that accounts for the ownership of the healthcare facility caring for TB patients. Categories for this variable include: public hospital, private religious hospital, or other private hospital.

Physician gender

This is a categorical variable with 1 indicating a male physician and 2 indicating a female physician caring for the TB patient.

Physician age

This is a numerical variable, calculated as the length of time in years between the study physician's date of birth and the date when TB is identified in a patient.

Physician specialty

This is a categorical variable that indicates the main licensed specialty of the physician.

3.3.5 Statistical Analysis Plan

Statistical Methods

Descriptive Analysis

To answer research question 1 and 2, numbers, percentages will be used to quantify the prevalence of TB in patient with and without mood disorder. Patient characteristics will also be described. Chi-square test for categorical variables are used to test the differences in the outcome variables (e.g., default status, mortality) between TB patients with and without mood disorder, as well as other covariates.

Moreover, differences in patient characteristics and outcome variables between subjects enrolled or not enrolled in the P4P on TB program are also be presented. The Chi-square test were also be used to test the significance of the differences. The table below describes how the results of the descriptive analysis will be presented.

Multivariate Regression and Logistic Model

To further answer research question 2, I regress various patient characteristic variables on TB patient mood disorder status to assess what patient characteristics are associated with the presence of mood disorder. Odds ratios, their 95% confidence intervals, and p values will be presented.

To examine whether TB patients with mood disorder have the same treatment default as TB patients without mood disorder, different models will be fit to match the traits of the outcome variables. Outcome variables of default status will be analyzed using multivariate logistic models to allow for adjustment of other covariates and confounders.

Cox Proportional Hazards Regression Models and Kaplan–Meier Method

The Kaplan–Meier method is used to estimate the survival rate and the log-rank test is used to examine the difference between the curves. By using univariable and multivariable Cox proportional hazards regression models, the relative hazard ratios (HRs) and the 95% confidence interval (CI) were calculated to examine the mortality of TB patients with and without mood disorder. The multivariable model controls for age, gender, income level, urbanization level and comorbidities with a significant difference in univariable Cox proportion hazards regression.

To answer research questions 5 and 6 regarding the effect of P4P on TB programs, we assess all study subjects from 2002-2010. Interaction terms of TB patient mood disorder status, treatment, hospital participation status in the P4P program will be used to compare the differences in the outcomes between P4P and non-P4P participating sites, and between TB patients with mood disorder and without mood disorder .

Random effects have considered and employed if there is medium to high levels of clustering among patients treated by the same physicians, the same health care facility, or in the same geographical area. Intra-class correlation coefficient (ICC) was used to report the magnitude of the clustering effect. Table 3.3 details the statistical analysis plan, including variables and statistical models proposed for each research question:

Table 3.3 Research Questions and Statistics

Study Aim	Research Question	Main Variables	Statistical Model
Aim 1	RQ1	Identification of mood disorder among TB patients	Descriptive analysis prevalence - using numbers and percentages
	RQ2	**Outcome variable** Mood disorder status among TB patients **Independent variables** Patient characteristics: age, gender, insurance premium, urbanization, disability, Charlson comorbidity index score, baseline comorbidities	Chi-square test to examine categorical variables, Multivariate logistic regression-adjusted odds ratio
Aim 2	RQ3	**Outcome variable** Default status	Multivariate logistic regression for default status
	RQ4	**Outcome variable** **Mortality**	Kaplan–Meier survival analysis and log-rank test Cox proportional hazard regression
		Main independent variables Mood disorder status P4P on TB **Other covariates** Patient characteristics: age, gender, insurance premium, urbanization, disability, Charlson comorbidity index score (CCI) Health care facility characteristics: ownership, accreditation level, geographical location Physician characteristics: age, gender, specialty	
Aim 3	RQ5	**Outcome variable** Default status	Multivariate logistic regression for default status

	RQ6	**Outcome variable** Mortality	Kaplan–Meier survival analysis and log-rank test ,Cox proportional hazard regression,
		Main independent variables Mood disorder status P4P on TB **Other covariates** Patient characteristics: age, gender, insurance premium, urbanization, disability, Charlson co-morbidity index score(CCI) Health care facility characteristics: ownership, accreditation level, geographical location Physician characteristics: age, gender, specialty	

3.3.6 Internal Validity and External Validity

The most critical threat to the internal validity of this study is that hospitals volunteer to participate in the P4P on TB program, which makes the P4P on TB program participation not an extraneous variable (Shi, 1997). In our study, the data provided by NHIRD is reported by health care facilities and supervised by the BNHI. The TCDC TB registry data are collected by the TB management system. No interviews, questionnaires, or tests used in this study. Therefore, testing and instrumentation treatment factors will not influence the internal validity of this study. History may be a threat to the internal validity. However, a group of control hospitals that did not participate in the P4P on TB program is included as a reference group, which may minimize the history threat.

The external validity of the study is relatively high because all TB patients will be observed and analyzed in the study. The study results are expected to reflect all of the TB patient population in Taiwan. However, the results may not be applicable to other geographic areas.

3.3.7 Ethical consideration

This study had been submitted to the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health. The JHSPH IRB reviewed and gave officially approval with IRB No: 00004870 on January 11, 2013. We used secondary datasets--the NHIRD and TCDC TB registry file, to conduct this study. Both datasets are managed by the governmental agencies. The National Health Research Institutes (NHRI) and Taiwan's Center for Disease Control (TCDC) encrypt and reconstruct the datasets before releasing the dataset to researchers. No personal identifiers will be included in any

of the datasets obtained. A pre-formatted agreement formulating the data use regulations of BNHI and NHRI and the Computer-Processed Personal Data Protection Act was signed between the researcher and the relevant government agencies. The researcher strictly adhered to all of the regulations. The study subjects bear no more than minimal risks.

4. CHAPTER FOUR: RESULTS

4.1 Study Aim 1:

To achieve the research aim 1) to investigate the prevalence and epidemiology of mood disorder, and examine patients' demographic characteristics and their relationship among TB patients in Taiwan, the research questions and hypotheses are:

Researcher question 1: What is the prevalence of mood disorder among TB patients in Taiwan?

Hypothesis 1: The prevalence of mood disorder is higher in TB patients than in the general population in Taiwan.

Results: During the study period, a total of 5,327 patients with TB were enrolled, and 1140 of the TB patients were diagnosed with mood disorder. The prevalence of mood disorder in years 2007 was 26.75% (796/2976). In the general population in Taiwan, the prevalence of mood disorder was 12.6% (111712/883453) in the same year. Thus, the prevalence of mood disorder in TB patients was two-fold higher than in the general population. The distribution of different types of mood disorder are listed in Table 4.1 and the trend is presented in Figure 4.1. About 83.4% of TB patients with mood disorder had anxiety and 26% had depression.

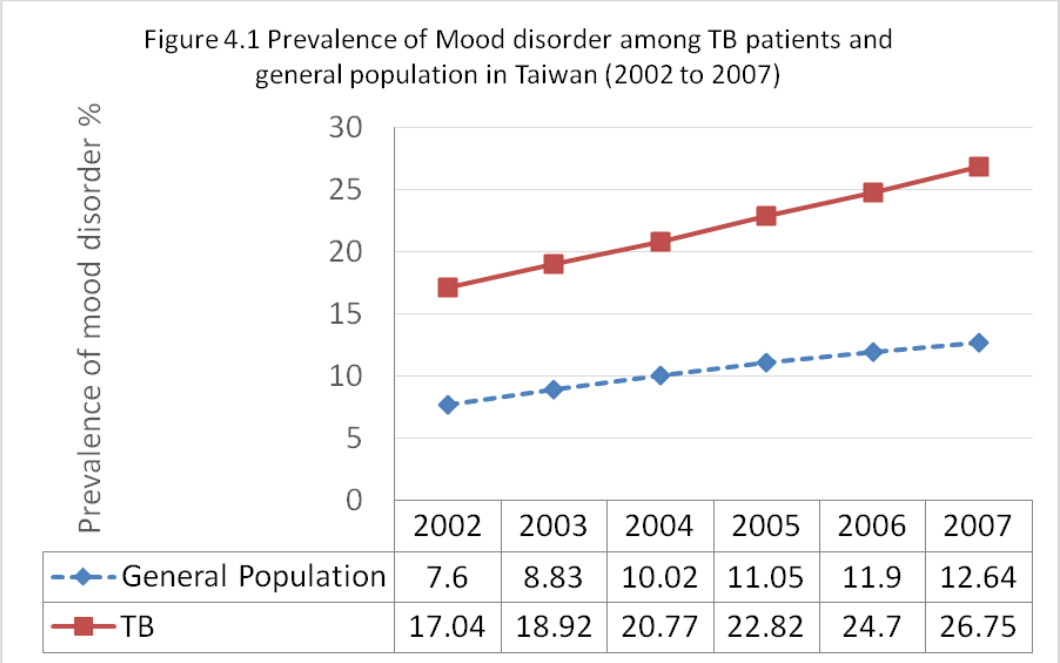


Figure 4.1 Prevalence of Mood disorder among TB patients and general population in Taiwan (2002 to 2007)

Table 4.1 Distribution of different type mood disorder

	N	%
Adjustment reaction	16	1.40
Bipolar	353	3.07
Depressive disorder	296	26.0
Anxiety	951	83.4

Research question 2: Among TB patients, what patient characteristics are associated with the presence of mood disorder in Taiwan?

Hypothesis 2 : Patient's age, gender, socio-economic status, location of residence, disease severity, and other co-morbidities are associated with the presence of mood disorder among TB patients.

Results: Table 4.2 shows that the comparison of mood status with TB patient characteristics and health status using logistic regression analysis. The results adjust for Charlson comorbidity index score (CCI) or comorbidities. The multivariable regression analysis indicates an increased risk of mood disorder in TB patients with the following characteristics:

1. Older age: TB patients older than 65 years of age have a significantly higher risk of mood disorder (OR = 2.79, 95% CI = 2.28–3.42, P< 0.001). There is also a trend of higher risk of having a mood disorder as age increases.

2. Female: women with TB have a higher probability of having a mood disorder than men (OR = 1.8, 95% CI = 1.57–2.07, P< 0.001).

3. Higher income: TB patients with higher income have a greater probability of having a mood disorder than lower income patients (OR = 1.35, 95% CI = 1.10–1.65, P< 0.01).

4. Disability: TB patients with a disability have a higher risk of having a mood disorder than TB patients without a disability (OR = 1.70, 95% CI = 1.36–1.65, P< 0.001).

5. Comobidities: TB patients with a higher Charlson comorbidity index score (CCI) may have a significantly higher chance of having a mood disorder. TB patients had a higher risk of mood disorder in terms of the following comorbidities: hypertension (OR = 1.77, 95% CI = 1.50–2.10, P< 0.001), diabetes (OR = 1.32, 95% CI = 1.13–1.55, P< 0.001),

CLD (chronic liver disease and cirrhosis) (OR = 1.90, 95% CI = 1.62–2.20, P< 0.001), and hyperlipidemia (OR = 1.26, 95% CI = 1.07–1.50, P< 0.01).

6. Patients in P4P participated hospital have a higher risk of having mood disorder than in non-P4P participants (OR = 1.15, 95% CI = 1.00–1.32, P< 0.05).

Table 4.2 Comparisons in the patients' demographic characteristics and health status in TB with or without mood disorder patients in logistic regression analysis

	Non-mood disorder N=4187 (78.6%)		mood disorder N=1140 (21.4%)			OR (95% CI)		
	N	%	N	%	p-value†	Crude	Model 1†	Model 2††
P4P					0.01			
No	2671	63.8	680	59.6		1.00	1.00	1.00
Yes	1516	36.2	460	40.4		1.19 (1.04-1.36)*	1.15 (1.00-1.32)*	1.15 (1.00-1.33)*
Patient characteristics								
Age, year					<0.0001			
<45	1331	31.8	170	14.9		1.00	1.00	1.00
45-65	1158	27.7	345	30.3		2.33 (1.91-2.85)***	2.21 (1.80-2.72)***	1.75 (1.41-2.18)***
>65	1698	40.6	625	54.8		2.88 (2.40-3.46)***	2.79 (2.28-3.42)***	2.03 (1.63-2.53)***
Means (SD)								
Gender					<0.0001			
Female=2	1419	33.9	495	43.4		1.50 (1.31-1.71)***	1.80 (1.57-2.07)***	1.79 (1.55-2.06)***
Male=1	2768	66.1	645	56.6		1.00	1.00	1.00
Insurance premium					0.06			
< 15,000	1405	33.6	344	30.2		1.00	1.00	1.00
NT$ 15,000-19,999	1961	46.8	576	50.5		1.20 (1.03-1.39)*	1.14 (0.98-1.33)	1.12 (0.96-1.31)
≧NT$ 20,000	821	19.6	220	19.3		1.09 (0.91-1.32)	1.35 (1.10-1.65)**	1.28 (1.04-1.58)*
Urbanization					0.85			
High	2139	51.1	586	51.4		1.00	--	--
Low	2048	48.9	554	48.6		0.99 (0.87-1.13)	--	--
Disability					<0.0001			
No	3891	92.9	991	86.9		1.00	1.00	1.00
Yes	296	7.07	149	13.1		1.98 (1.60-2.44)***	1.70 (1.36-1.65)***	1.62 (1.30-2.03)***
Charlson comorbidity index score					<0.0001			
0	2743	65.5	590	51.8		1.00	1.00	--
1	578	13.8	215	18.9		1.73 (1.44-2.07)***	1.36 (1.12-1.65)**	--
2	370	8.84	158	13.9		1.99 (1.62-2.44)***	1.48 (1.19-1.84)***	--
3+	496	11.9	177	15.5		1.66 (1.37-2.01)***	1.14 (1.10-1.42) *	--
Baseline Comorbidities								
Hypertension					<0.0001			
No	2620	62.6	457	40.1		1.00	--	1.00

Yes	1567	37.4	683	59.9		2.50 (2.19-2.86)***	--	1.77 (1.50-2.10)***
Diabetes					0.0005			
No	3388	80.9	869	76.2		1.00	--	1.00
Yes	799	19.1	271	23.8		1.32 (1.13-1.55)***	--	0.80 (0.67-0.95)*
Hyperlipidemia					<0.0001			
No	3459	82.6	801	70.3		1.00	--	1.00
Yes	728	17.4	339	29.7		2.01 (1.73-2.34)***	--	1.26 (1.07-1.50)**
CKD					0.003			
No	4032	96.3	1075	94.3		1.00	--	1.00
Yes	155	3.70	65	5.70		1.57 (1.17-2.12)**	--	0.98 (0.71-1.34)
CLD					<0.0001			
No	3343	79.8	740	64.9		1.00	--	1.00
Yes	844	20.2	400	35.1		2.14 (1.86-2.47)***	--	1.90 (1.62-2.20)***
HIV infection					0.051			
No	4173	99.7	1140	100.0		1.00	--	--
Yes	14	0.33	0	0.00		--	--	--
Schizophrenia					0.95			
No	4162	99.4	1133	99.4		1.00	--	--
Yes	25	0.60	7	0.61		1.03 (0.44-2.39)	--	--
Hospital characteristics								
Hospital level					0.97			
Medical center	1502	35.9	401	35.2		0.99 (0.78-1.25)	--	--
District hospital	1361	32.5	378	33.2		1.02 (0.81-1.30)	--	--
Regional hospital	911	21.8	249	21.8		1.01 (0.78-1.30)	--	--
Others	413	9.86	112	9.82		1.00	--	--
Hospital ownership					0.99			
Public	1611	38.5	439	38.5		1.00	--	--
Private religious	2251	53.8	611	53.6		1.02 (0.79-1.31)	--	--
Other private	325	7.76	90	7.89		1.00 (0.87-1.14)	--	--
Geographic location					0.09			
Taipei	975	23.3	261	22.9		1.00	--	--
Northern	545	13.0	130	11.4		0.89 (0.70-1.13)	--	--
Central	794	19.0	258	22.6		1.21 (0.99-1.48)	--	--
Southern	717	17.1	194	17.0		1.01 (0.82-1.25)	--	--
Kao-Ping	914	21.8	228	20.0		0.93 (0.76-1.14)	--	--
Eastern	242	5.78	69	6.05		1.07	--	--

						(0.79-1.44)		
Physician characteristics								
Age, year					0.67			
< 35	617	14.7	161	14.1		1.00	--	--
35-64	3523	84.1	969	85.0		1.05 (0.87-1.27)	--	--
>= 65	47	1.12	10	0.88		0.82 (0.40-1.65)	--	--
Gender					0.93			
Female=2	242	5.79	65	5.72		1.00	--	--
Male=1	3941	94..2	1072	94.3		1.01 (0.76-1.34)	--	--
Specialty					0.70			
Chest Medicine	1757	42.0	487	42.7		1.00	--	--
Infectious Disease	165	3.94	46	4.04		1.01 (0.72-1.42)	--	--
Family Medicine	157	3.75	40	3.51		0.92 (0.64-1.32)	--	--
Tuberculosis Specialist	1006	24.0	290	25.4		1.04 (0.88-1.23)	--	--
General Medicine	673	16.1	176	15.4		0.94 (0.78-1.15)	--	--
Other	429	10.3	101	8.86		0.85 (0.70-1.08)	--	--

†Chi-square test, t-test and logistic regression

†Mode 1 was adjusted by patient characteristics , physician and practice characteristics, P4P participation and Charlson comorbidity index score (CCI) ††Mode 2 was adjusted for patient characteristics , physician and practice characteristics, P4P participation and baseline comorbidities

* p< 0.05, ** p < 0.01, *** p < 0.001.

4.2 Study Aim 2:

To achieve research **aim 2**) to evaluate the impact of mood disorder on TB treatment default and P4P effect on TB patients, the research questions and hypotheses are:

Research question 3: Do TB patients with mood disorder have the same rate of treatment default rate as TB patients without mood disorder in Taiwan?

Hypothesis 3: TB patients with mood disorder have a higher default rate than TB patients without mood disorder in Taiwan.

Results:

Mood Disorder and Patient's Default

Patient characteristics and default

Table 4.3 presents the relationship of patients' default from TB treatment and associated factors in the logistic regression analysis. The default rates are based on patient characteristics (age, gender, SES, disability status, co-morbidity level and P4P participation), as well as physician and practice characteristics (physician age, gender, specialty, accreditation level of practice setting, ownership of the practice, and geographic area).Mood disorder TB patients had significant higher default than non-mood disorder TB patients (OR=1.37, 95% CI 1.17 -1.59)..

According to Table 4.4, the default rate from TB treatment varies based on patient characteristics. The crude odds ratio for the age factor for non- mood disorder patients younger than 45 years of age suggests a higher risk for default (47.6%, crude (OR=1.51, 95% CI 1.30-1.74, $p < 0.001$). However, after controlling for other patient characteristics, and physician and hospital characteristics, the odds ratio of for the $<$ 45 years old group

was 1.14 (95% CI =0.94-1.37). Therefore, age of the patient seems to not have an effect on patients' default from TB treatment.

The odds ratio of default comparing females versus males in the mood disorder group, after considering confounding variables, was 1.38 (95% 1.05-1.81)($p < 0.05$). The non-mood disorder group has similar results (OR=1.66, 95% CI 1.43-1.92, $p < 0.001$). Hence, female patients had significantly higher default rates than male patients in both the mood disorder and non-mood disorder group.

Looking at patients' socio-economic variables by comparing insurance premiums, patients with the insurance premium NTD 15,000-19,999 had significantly less default rates than patients with the insurance premium ≧NTD 20,000 in the non-mood disorder group. However, there were no significant differences in the mood disorder group. There was also no difference in default rates between patients living in urban or rural areas in both mood disorder and non-mood disorder groups.

Level of patients' physical condition was determined by their disability and comorbidity. Higher CCI score represents more serious medical condition. Patients' disability had no influence on their default from TB treatment. However, using CCI to identify the relationship between patient's comorbidity level and default rate, we see that higher CCI was associated with lower default from treatment in the non-mood disorder group, after adjusting for other variables. There was no difference in mood group.

Hospital and physician characteristics with default

For accreditation level of practice setting, hospitals below the regional hospital level had a significantly higher default rate than medical centers in both mood disorder

and non-mood disorder group. Private hospitals had lower default rate than public hospitals. Using Taipei as a reference city, hospitals located in Northern and in Eastern branch had lower default rate than Taipei.

For physician characteristics, physician age and gender had no effect in patient default. Family medicine doctors had significantly higher default rate (OR=2.66, 95% CI=1.06-6.71, P< 0.05 in mood disorder; OR=1.70, 95% CI=1.11-2.59, P< 0.05 in non-mood disorder) than chest doctors.

Table 4.3 Results of the impact of mood disorder on TB treatment default and associated risk factor among TB patients using logistic regression analysis

	TB patients default		OR (95% CI)		
	N	%	Crude	Model 1	Model 2
Patient characteristics					
Mood disorder					
No	1769	42.3	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	540	47.4	1.23 (1.08-1.40)**	1.37 (1.17-1.59)***	1.35 (1.16-1.57)***
P4P					
No	1937	57.9	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	370	18.7	0.17 (0.15-0.19)***	0.18 (0.16-0.21)***	0.18 (0.16-0.21)***
Age, year					
<45	709	47.2	1.36 (1.19-1.55)***	1.10 (0.93-1.30)	1.15 (0.96-1.37)
45-65	678	45.1	1.25 (1.10-1.42)***	1.15 (0.98-1.35)	1.22 (1.04-1.43)*
>65	922	39.7	1.00 (reference)	1.00 (reference)	1.00 (reference)
Gender					
Female=2	989	51.7	1.70 (1.51-1.90)***	1.59 (1.39-1.80)***	1.59 (1.40-1.81)***
Male=1	1320	38.7	1.00 (reference)	1.00 (reference)	1.00 (reference)
Insurance premium					
< 15,000	793	45.3	1.23 (1.08-1.39)**	1.26 (1.09-1.45)**	1.25 (1.09-1.45)**
NT$ 15,000-19,999	1024	40.4	1.00 (reference)	1.00 (reference)	1.00 (reference)
>=NT$ 20,000	492	47.3	1.32 (1.15-1.530***	1.31 (1.11-1.55)**	1.32 (1.11-1.56)**
Urbanization					
High	1223	44.9	1.14 (1.02-1.27)*	1.04 (0.91-1.19)	1.06 (0.92-1.21)
Low	1086	41.7	1.00 (reference)	1.00 (reference)	1.00 (reference)
Disability					
No	2116	43.3	1.00 (reference)	--	--
Yes	193	43.4	1.00 (0.82-1.22)	--	--
Charlson comorbidity index score					
0	1557	46.7	1.46 (1.22-1.73)***	1.25 (1.02-1.54)*	--
1	303	38.2	1.03 (0.83-1.27)	1.12 (0.88-1.42)	--
2	196	37.1	0.98 (0.77-1.24)	0.96 (0.74-1.25)	--
3+	253	37.6	1.00 (reference)	1.00 (reference)	--
Baseline Comorbidities					
Hypertension					
No	1386	45.0	1.00 (reference)	--	1.00 (reference)
Yes	923	41.0	0.85 (0.76-0.95)**	--	1.06 (0.92-1.21)
Diabetes					
No	1938	45.5	1.00 (reference)	--	1.00 (reference)
Yes	371	34.7	0.64 (0.55-0.73)***	--	0.72 (0.61-0.84)***
Hyperlipidemia					

No	1837	43.1	1.00 (reference)	--	--
Yes	472	44.2	1.05 (0.91-1.20)	--	--
CKD					
No	2231	43.7	1.00 (reference)	--	1.00 (reference)
Yes	78	35.5	0.71 (0.53-0.94)*	--	0.84 (0.61-1.15)
CLD					
No	1781	43.6	1.00 (reference)	--	--
Yes	528	42.4	0.95 (0.84-1.08)	--	--
HIV infection					
No	2306	43.4	1.00 (reference)	--	--
Yes	3	21.4	0.36 (0.10-1.28)	--	--
Schizophrenia					
No	2291	43.3	1.00 (reference)	--	--
Yes	18	56.3	1.69 (0.84-3.40)	--	--
Hospital characteristics					
Hospital level					
Medical center	762	40.0	1.32 (1.15-1.51)***	0.96 (0.81-1.12)	0.94 (0.80-1.11)
District hospital	585	33.6	1.00 (reference)	1.00 (reference)	1.00 (reference)
Regional hospital	625	53.9	2.30 (1.98-2.68)***	1.57 (1.31-1.89)***	1.57 (1.30-1.89)***
Others	337	64.2	3.54 (2.88-4.34)***	1.34 (0.88-2.03)	1.39 (0.92-2.10)
Hospital ownership					
Public	959	46.8	3.11 (2.51-3.86)***	1.37 (1.19-1.57)***	1.36 (1.18-1.57)***
Private religious	1079	37.7	1.00 (reference)	1.00 (reference)	1.00 (reference)
Other private	271	65.3	1.45 (1.30-1.63)***	1.94 (1.24-3.04)**	1.86 (1.19-2.92)**
Geographic location					
Taipei	569	46.0	1.72 (1.33-2.34)***	1.94 (1.42-2.64)***	1.98 (1.45-2.69)***
Northern	234	34.7	1.07 (0.81-1.42)	1.08 (0.79-1.49)	1.10 (0.80-1.51)
Central	436	41.4	1.43 (1.10-1.87)**	2.27 (1.68-3.07)***	2.28 (1.68-3.08)***
Southern	404	44.4	1.61 (1.23-2.11)***	1.49 (1.10-2.04)*	1.50 (1.10-2.04)*
Kao-Ping	563	49.3	1.96 (1.51-2.55)***	1.89 (1.40-2.54)***	1.92 (1.43-2.58)***
Eastern	103	33.1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Physician characteristics					
Age, year					
< 35	315	40.5	1.00 (reference)	1.00 (reference)	1.00 (reference)
35-64	1962	43.7	1.14 (0.98-1.33)	1.05 (0.89-1.26)	1.05 (0.88-1.25)
>= 65	32	56.1	1.88 (1.09-3.24)*	1.12 (0.61-2.06)	1.10 (0.60-2.04)
Gender					
Female=2	120	39.1	1.00 (reference)	--	--
Male=1	2183	43.6	1.20 (0.95-1.52)	--	--
Specialty					

Chest Medicine	750	33.4	1.54 (1.11-2.13)**	1.65 (1.16-2.34)**	1.65 (1.16-2.35)**
Infectious Disease	52	24.6	1.00 (reference)	1.00 (reference)	1.00 (reference)
Family Medicine	145	73.6	8.53 (5.46-13.3)***	3.02 (1.83-4.97)***	3.10 (1.88-5.11)***
Tuberculosis Specialist	719	55.5	3.81 (2.74-5.31)***	2.10 (1.46-3.04)***	2.09 (1.45-3.02)***
General Medicine	378	44.5	2.45 (1.75-3.45)***	1.32 (0.90-1.93)	1.31 (0.90-1.92)
Other	265	50.0	3.06 (2.14-4.37)***	1.45 (0.98-2.16)	1.45 (0.98-2.15)

†Chi-square, logistic regression analysis

Mode 1 adjusted for patient characteristics , physician and practice characteristics, P4P participation and Charlson comorbidity index score (CCI) ††Mode 2 adjusted for characteristics , physician and practice characteristics, P4P participation and baseline comorbidities

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 4.4 Results of comparing TB with and without mood disorder patients default from treatment and associated risk factor using logistic regression analysis

	TB patients with mood disorder				TB patients without mood disorder			
	N	**%**	**Crude**	**Model†**	**N**	**%**	**Crude**	**Model†**
P4P								
No	430	63.2	1.00	1.00	1509	56.5	1.00	1.00
Yes	110	23.9	0.18 (0.14-0.24)***	0.20 (0.15-0.26)***	260	17.2	0.16 (0.14-0.19)***	0.17 (0.15-0.21)***
All	540	47.4			1769	42.3		
Patient characteristics								
Age, year								
< 45	76	44.7	0.97 (0.60-1.37)	0.79 (0.52-1.18)	633	47.6	1.51 (1.30-1.74)***	1.14 (0.94-1.37)
45-64	180	52.2	1.31 (1.04-1.71)*	1.25 (0.92-1.70)	498	43.0	1.25 (1.08-1.46)**	1.12 (0.93-1.35)
>= 65	284	45.4	1.00	1.00	638	37.6	1.00	
Gender (male vs. female)								
Female	259	52.3	1.42 (1.12-1.80)**	1.38 (1.05-1.81)*	730	51.4	1.76 (1.55-2.01)***	1.66 (1.43-1.92)***
Male	281	43.6	1.00	1.00	1039	37.5	1.00	1.00
Insurance premium (NT$)								
< 15,000	174	50.6	0.97 (0.69-1.36)	--	619	44.1	0.92 (0.77-1.09)	0.93 (0.76-1.13)
15,000-19,999	253	43.9	0.74 (0.54-1.01)	--	771	39.3	0.76 (0.64-0.89)***	0.75 (0.62-0.91)**
>= 20,000	113	51.4	1.00	--	379	46.2	1.00	1.00
Urbanization								
High	291	49.7	1.21 (0.96-1.53)	--	932	43.6	1.12 (0.9-1.26)	--
Low	249	45.0	1.00	--	837	40.9	1.00	--
Disability								
No	472	47.6	1.00	--	1644	42.3	1.00	--
Yes	68	45.6	0.92 (0.65-1.30)	--	125	42.2	1.00 (0.79-1.27)	--
Charlson comorbidity index score								
0	297	50.3	1.00	1.00	1260	45.9	1.00	1.00
1	86	40.0	0.65 (0.48-0.90)**	0.94 (0.64-1.36)	217	37.5	0.71 (0.59-0.85)***	0.89 (0.72-1.11)
2	75	47.5	0.89 (0.63-1.27)	1.02 (0.68-1.53)	121	32.7	0.57 (0.46-0.72)***	0.68 (0.52-0.89)**
3+	82	46.3	0.85 (0.61-1.19)	1.03 (0.69-1.54)	171	34.5	0.62 (0.51-0.76)***	0.73 (0.58-0.93)*
Hospital characteristics								
Hospital level								
Medical center	170	42.4	1.00	1.00	592	39.4	1.00	1.00
District hospital	141	37.3	0.81 (0.61-1.08)	1.25 (0.88-1.77)	444	32.6	0.74 (0.64-0.87)***	1.00 (0.83-1.20)
Regional hospital	148	59.4	1.99 (1.44-2.75)***	2.09 (1.39-3.15)***	477	52.4	1.69 (1.43-2.00)***	1.53 (1.24-1.89)***

Others	81	72.3	3.55 (2.24-5.62)***	1.65 (0.64-4.24)	256	62.0	2.51 (2.00-3.14)***	1.30 (0.81-2.07)
Hospital ownership								
Public	229	52.2	1.00	1.00	730	45.3	1.00	1.00
Private religious	245	40.1	0.61 (0.48-0.79)***	0.64 (0.47-0.87)**	734	37.1	0.71 (0.62-0.81)***	0.75 (0.64-0.88)***
Other	66	73.3	2.52 (1.52-4.17)***	1.25 (0.46-3.39)	205	63.1	2.06 (1.61-2.64)***	1.49 (0.92-2.42)
Geographic location								
Taipei	144	55.2	1.00	1.00	425	43.6	1.00	1.00
Northern	51	39.2	0.53 (0.34-0.81)**	0.38 (0.23-0.64)***	183	33.6	0.65 (0.53-0.81)***	0.61 (0.48-0.79)***
Central	120	46.5	0.71 (0.50-0.99)*	0.73 (0.49-1.10)	316	39.8	0.86 (0.71-1.04)	1.29 (1.02-1.62)*
Southern	96	49.5	0.80 (0.55-1.16)	0.53 (0.33-0.85)**	308	43.0	0.98 (0.80-1.18)	0.82 (0.64-1.05)
Kao-Ping	104	45.6	0.68 (0.48-0.97)*	0.55 (0.36-0.84)**	459	50.2	1.31 (1.09-1.57)**	1.10 (0.89-1.36)
Eastern	25	36.2	0.46 (0.27-0.80)**	0.43 (0.22-0.82)*	78	32.2	0.62 (0.46-0.83)**	0.52 (0.37-0.72)***
Physician characteristics								
Age, year								
< 35	60	37.3	1.00	1.00	255	41.3	1.00	--
35-64	473	48.8	1.61 (1.14-2.26)**	1.52 (1.03-2.25)*	1489	42.3	1.04 (0.87-1.24)	--
>=65	7	70.0	3.93 (0.98-15.8)	2.12 (0.48-9.32)	25	53.2	1.61 (0.89-2.93)	--
Gender								
Female	25	38.5	1.00	--	95	39.3	1.00	--
Male	513	47.9	1.47 (0.88-2.46)	--	1670	42.4	1.14 (0.87-1.48)	--
Specialty								
Chest Medicine	182	37.4	1.00	1.00	568	32.3	1.00	1.00
Infectious Disease	15	32.6	0.81 (0.43-1.54)	1.07 (0.53-2.14)	37	22.4	0.61 (0.41-0.88)**	0.50 (0.33-0.75)***
Family Medicine	33	82.5	7.90 (3.42-18.2)***	2.66 (1.06-6.71)*	112	71.3	5.21 (3.64-7.47)***	1.70 (1.11-2.59)*
General Medicine	91	51.7	1.79 (1.27-2.54)**	0.83 (0.54-1.27)	287	42.6	1.56 (1.30-1.87)***	0.79 (0.63-0.99)*
Other	58	57.4	2.26 (1.46-3.49)***	1.05 (0.62-1.77)	207	48.3	1.95 (1.58-2.42)***	0.84 (0.65-1.08)

Model[†] adjusted odds ratio: multivariable analysis including patient characteristics (age, gender, SES, disability status, co-morbidity level and P4P participation), physician and practice characteristics (physician age, gender, specialty, accreditation level of practice setting, ownership of the practice, and geographic area).
* p<0.05, ** p<0.01, ***p<0.001

Table 4.5 Results of logistic regression analysis with TB patients default from treatment stratified by patient, Hospital, and Physician characteristics

	TB patients with mood disorder					TB patients without mood disorder				
	Non-P4P		P4P			Non-P4P		P4P		
	N	%	Event no	%	Model	N	%	Event no	%	Model
Patient characteristics										
Age, year										
< 45	62	57.9	14	22.2	0.16 (0.07-0.38)***	550	60.7	83	19.5	0.17 (0.13-0.24)***
45-64	149	69.3	31	23.9	0.09 (0.05-0.17)***	427	57.3	71	17.2	0.14 (0.10-0.20)***
>= 65	219	61.2	65	24.3	0.26 (0.18-0.39)***	532	52.2	1006	15.6	0.20 (0.16-0.26)***
Gender(male vs. female)										
Female	209	67.4	50	27.0	0.15 (0.10-0.25)***	644	66.6	86	19.0	0.12 (0.09-0.16)***
Male	221	59.7	60	21.8	0.24 (0.16-0.36)***	865	50.8	174	16.4	0.21 (0.17-0.26)***
Insurance premium (NT$)										
< 15,000	138	64.5	36	27.7	0.24 (0.14-0.41)***	530	58.2	89	18.0	0.18 (0.14-0.24)***
15,000-19,999	196	60.1	57	22.8	0.22 (0.14-0.34)***	657	53.2	114	15.7	0.18 (0.14-0.23)***
>= 20,000	96	68.6	17	21.3	0.08 (0.03-0.18)***	622	61.3	57	19.3	0.13 (0.09-0.20)***
Urbanization										
High	229	63.6	62	27.4	0.18 (0.12-0.28)***	786	56.9	146	19.3	0.18 (0.14-0.23)***
Low	201	62.8	48	20.5	0.20 (0.13-0.31)***	723	56.1	114	15.0	0.16 (0.13-0.21)***
Disability										
No	376	63.6	96	24.0	0.19 (0.14-0.26)***	1403	56.6	241	17.1	0.18 (0.15-0.21)***
Yes	54	60.7	14	23.3	0.30 (0.11-0.85)*	106	55.8	19	17.9	0.16 (0.08-0.31)***
Charlson comorbidity index score										
0	250	67.2	47	21.6	0.14 (0.09-0.22)***	1096	59.9	164	17.9	0.15 (0.12-0.19)***
1	57	53.3	29	26.9	0.33 (0.16-0.68)**	171	51.4	46	18.8	0.25 (0.16-0.40)***
2	59	59.6	16	27.1	0.14 (0.05-0.38)***	101	46.5	20	13.1	0.14 (0.08-0.27)***
3+	64	62.8	18	24.0	0.25 (0.10-0.59)**	141	48.3	30	14.7	0.21 (0.12-0.36)***
Hospital characteristics										
Hospital level										
Medical center	126	54.1	44	26.2	0.31 (0.18-0.53)***	494	52.1	98	17.7	0.21 (0.16-0.29)***
District hospital	99	57.9	42	20.3	0.20 (0.12-0.34)***	331	48.2	113	16.8	0.21 (0.16-0.27)***
Regional hospital	128	71.1	20	29.0	0.15 (0.08-0.30)***	437	62.3	40	19.1	0.13 (0.09-0.20)***
Others	77	80.2	4	25.0	0.12	247	73.7	9	11.5	0.08

					(0.02-0.57)**					(0.03-0.18)***
Hospital ownership										
Public	169	66.5	60	32.4	0.25 (0.16-0.40)***	612	61.5	118	19.2	0.17 (0.13-0.23)***
Private religious	198	56.7	47	17.9	0.17 (0.11-0.26)***	696	49.2	138	16.5	0.21 (0.17-0.27)***
Other	63	81.8	3	23.1	0.16 (0.02-1.32)	201	77.0	4	6.25	0.03 (0.01-0.10)***
Geographic location										
Taipei	108	68.4	36	35.0	0.19 (0.10-0.36)***	359	58.3	66	18.4	0.16 (0.11-0.22)***
Northern	41	47.1	10	23.3	0.65 (0.21-1.99)	150	43.6	33	16.4	0.37 (0.22-0.63)***
Central	96	70.1	24	19.8	0.11 (0.06-0.22)***	245	62.8	71	17.6	0.16 (0.11-0.24)***
Southern	81	70.4	15	19.0	0.13 (0.06-0.30)***	271	57.5	37	15.0	0.15 (0.10-0.23)***
Kao-Ping	88	59.9	16	19.8	0.22 (0.10-0.49)***	419	60.6	40	17.9	0.15 (0.10-0.23)***
Eastern	16	44.4	9	27.3	0.32 (0.03-3.01)	70	84.3	13	15.7	0.28 (0.12-0.64)**
Physician characteristics										
Age, year										
< 35	47	50.0	13	19.4	0.42 (0.16-1.06)	223	54.1	32	15.6	0.1 (0.10-0.27)***
35-64	376	65.1	97	24.8	0.18 (0.13-0.25)***	1261	56.6	228	17.6	0.18 (0.15-0.21)***
>=65	7	87.5	0	0.00	--	25	810.7	0	0.00	--
Gender										
Female	17	53.1	8	24.2	0.15 (0.02-1.24)	82	59.0	13	12.6	0.09 (0.04-0.24)***
Male	411	63.7	102	23.9	0.19 (0.14-0.26)***	1423	56.3	247	17.5	0.18 (0.15-0.21)***
Specialty										
Chest Medicine	120	58.3	62	22.1	0.21 (0.14-0.33)***	387	50.2	181	18.4	0.24 (0.19-0.30)***
Infectious Disease	3	23.1	12	36.4	1.13 (0.06-22.5)	30	34.9	7	8.86	0.11 (0.03-0.40)***
Family Medicine	32	84.2	1	50.0	--	112	76.2	0	0.00	--
General Medicine	70	58.8	21	36.8	0.39 (0.18-0.86)*	2045	50.9	42	21.9	0.30 (0.20-0.46)***
Other	55	64.0	3	20.0	0.07 (0.01-0.51)**	201	53.7	6	10.9	0.08 (0.03-0.20)***

†Mode 1 was adjusted by patient characteristics , physician and practice characteristics and Charlson comorbidity index score (CCI)

* p<0.05, ** p<0.01, ***p<0.001

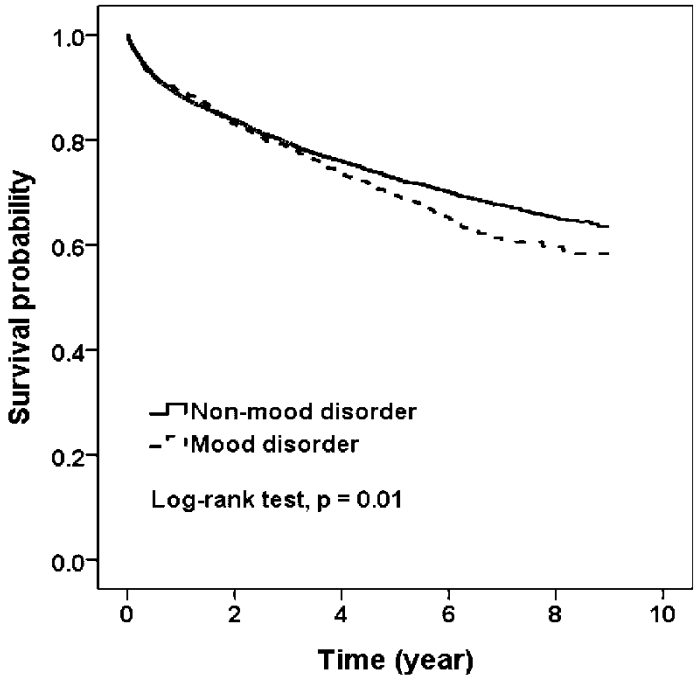
Research question4: Do TB patients with mood disorder have the same mortality as TB patients without mood disorder in Taiwan?

Hypothesis 4: TB patients with mood disorder have a higher mortality rate than TB patients without mood disorder in Taiwan.

Results:

Mortality of TB patients with mood disorder

To investigate the mortality of TB patients with mood disorder, Cox proportional hazard models were used to identify associated risk factors, the effect of P4P enrollment, and the overall survival of TB patients with mood disorder. In this study, we traced the mortality of enrollees from the year 2002 to the end of 2010. In the nine-year period, 376 (33%) TB patients with mood disorder died, while 1232 (29.4)% TB patients without mood disorder died. Thus the all-cause mortality rate of TB patients with mood disorder was higher than that of non-mood disorder patients. The Kaplan–Meier survival analysis showed that the survival rate was lower in TB patients with mood disorder than in the non-mood disorder patients (log-rank test $p < 0.05$). Time series tables and survival curves containing detailed descriptions of time to event (death) can be found in Figure 4.2. The log-rank test indicates that TB patients with mood disorder had significantly lower survival rates than non-mood disorder patients ($P = 0.01$, $p < 0.05$).



Mood disorder					
Population at risk	1140	946	659	331	105
Event no.	197	97	62	21	2
Non-mood-disorder					
Population at risk	4187	3511	2569	1481	491
Event no.	676	315	163	71	7

Figure 4.2 Survival probability between TB patients with and without mood disorder using Kaplan-Meier analysis

The mortality of TB patients

We examined the mortality of TB enrollees from the year 2002 to the end of 2010. Table 4.6 and 4.7 present patient mortality data and related risk factors for patients with only TB, using Cox proportional hazards regression model. Regarding TB patients' demographic factors, we did find a trend of increased number, proportion, or hazard ratios of deaths in the elderly, male, low income, disabled, or those with different CCI scores. After adjustment, patients older than 65 years of age had a greater risk (8.47 times) of mortality than patients younger than 45 years of age (HR=8.47, 95% CI = 6.79–10.6, P < 0.001). Patients with higher CCI scores also had a significantly higher hazard ratio than patients with a CCI score of zero (HR=4.7, 95% CI = 4.09–5.39, P< 0.001). The comorbidities of hypertension, diabetes, and chronic kidney disease contributed to a significantly high risk of death. There were no significant differences in mortality rate by hospital accreditation level. Private hospitals has lower mortality than public hospitals (HR=0.88, 95% CI = 0.79–0.99, P< 0.05). Hospitals located in southern and Kao-ping branch had higher mortality rates than hospitals in Taipei (in southern HR=1.27, 95% CI = 1.06–1.52, P< 0.01; in Kao-ping HR=1.18, 95% CI = 1.00–1.38, P< 0.05). TB patients with male physicians had higher mortality rates than TB patients with female physicians. Infectious disease physicians had significantly higher risk of patient mortality than other specialties. It may be that TB patients in the infectious disease department had more complex conditions.

Table 4.6 Mortality and associated risk factor in TB patients using Cox proportional hazard regression

			HR (95% CI)		
	N	%	Crude	Model 1	Model 2
Patient characteristics					
Mood disorder					
No	1232	61.69	1.00	1.00	1.00
Yes	376	72.57	1.16 (1.03-1.30)*	1.80 (1.61-1.90)***	1.84 (1.70-1.95)**
P4P					
No	1013	60.05	1.00	1.00	1.00
Yes	595	71.84	1.11 (1.01-1.23)*	0.93 (0.83-1.05)	0.96 (0.86-1.08)
Age, year					
<45	97	11.41	1.00	1.00	1.00
45-65	287	36.63	3.16 (2.51-3.98)***	2.45 (1.94-3.09)***	2.89 (2.28-3.66)***
>65	1224	138.81	11.4 (9.23-14.0)***	6.03 (4.85-7.49)***	8.47 (6.79-10.6)***
Gender					
Female=2	422	44.80	1.00	1.00	1.00
Male=1	1186	75.40	1.66 (1.49-1.86)***	1.28 (1.15-1.44)***	1.34 (1.20-1.50)***
Insurance premium					
< 15,000	651	83.50	2.75 (2.32-3.26)***	1.61 (1.34-1.92)***	1.80 (1.51-2.16)***
NT$ 15,000-19,999	794	67.21	2.23 (1.88-2.64)***	1.35 (1.13-1.61)***	1.43 (1.20-1.70)***
>=NT$ 20,000	163	29.42	1.00	1.00	1.00
Urbanization					
High	737	56.01	1.00	1.00	1.00
Low	871	72.63	1.28 (1.16-1.41)***	0.98 (0.87-1.09)	1.07 (0.96-1.19)
Disability					
No	1370	58.14	1.00	1.00	1.00
Yes	238	149.96	2.43 (2.11-2.78)***	1.45 (1.26-1.68)***	1.91 (1.66-2.21)***
Charlson comorbidity index score					
0	487	26.99	1.00	1.00	--
1	339	100.17	3.58 (3.11-4.11)***	2.18 (1.88-2.51)***	--
2	289	148.83	5.21 (4.51-6.03)***	3.03 (2.60-3.53)***	--
3+	493	276.89	9.11 (8.03-10.3)***	4.70 (4.09-5.39)***	--
Baseline Comorbidities					
Hypertension					
No	598	37.45	1.00	--	1.00
Yes	1010	109.97	2.80 (2.53-3.10)***	--	1.15 (1.02-1.29)*
Diabetes					
No	1139	54.69	1.00	--	1.00

Yes	469	108.43	1.90 (1.70-2.11)***	--	1.26 (1.12-1.41)***
Hyperlipidemia					
No	1287	63.71	1.00	--	--
Yes	321	64.85	1.01 (0.89-1.14)	--	--
CKD					
No	1479	60.56	1.00	--	1.00
Yes	129	177.48	2.68 (2.24-3.21)***	--	1.43 (1.19-1.73)***
CLD					
No	1169	60.06	1.00	--	1.00
Yes	439	77.20	1.27 (1.14-1.42)***	--	1.02 (0.91-1.14)
HIV infection					
No	1604	63.93	1.00	--	--
Yes	4	65.72	1.00 (0.38-2.67)	--	--
Schizophrenia					
No	1603	64.28	1.00	--	1.00
Yes	5	23.38	0.40 (0.17-0.97)*	--	0.67 (0.27-1.61)
Hospital characteristics					
Hospital level					
Medical center	594	65.37	1.00	1.00	1.00
District hospital	523	65.91	0.99 (0.88-1.11)	1.11 (0.97-1.26)	1.07 (0.94-1.22)
Regional hospital	388	72.96	1.11 (0.98-1.26)	1.10 (0.94-1.28)	1.09 (0.93-1.27)
Others	103	36.64	0.58 (0.47-0.71)***	0.98 (0.66-1.45)	0.73 (0.49-1.07)
Hospital ownership					
Public	78	35.64	1.00	1.00	1.00
Private religious	835	61.36	0.83 (0.75-0.92)***	0.94 (0.84-1.06)	0.88 (0.79-0.99)*
Other private	695	74.30	0.49 (0.39-0.62)***	0.73 (0.49-1.11)	0.86 (0.57-1.31)
Geographic location					
Taipei	332	53.53	1.00	1.00	1.00
Northern	161	50.01	0.91 (0.75-1.10)	0.97 (0.80-1.19)	1.07 (0.88-1.31)
Central	326	67.24	1.22 (1.05-1.42)*	1.08 (0.91-1.29)	1.18 (0.99-1.41)
Southern	351	87.90	1.59 (1.37-1.85)***	1.14 (0.96-1.37)	1.27 (1.06-1.52)**
Kao-Ping	354	66.67	1.22 (1.05-1.41)*	1.08 (0.92-1.26)	1.18 (1.00-1.38)*
Eastern	84	53.25	0.99 (0.78-1.26)	0.97 (0.75-1.25)	1.08 (0.83-1.40)
Physician characteristics					
Age, year					
< 35	236	65.11	1.00	1.00	1.00
35-64	1365	64.47	0.99 (0.87-1.14)	1.05 (0.91-1.22)	1.05 (0.91-1.21)
>= 65	7	19.80	0.33 (0.16-0.69)**	0.51 (0.24-1.10)	0.52 (0.24-1.12)
Gender					
Female=2	556	37.24	1.00	1.00	1.00

Male=1	1547	65.47	1.76 (1.35-2.30)***	1.40 (1.06-1.84)*	1.49 (1.13-1.96)**
Specialty					
Chest Medicine	642	63.10	1.00	1.00	1.00
Infectious Disease	74	83.61	1.30 (1.03-1.66)*	1.32 (1.04-1.69)*	1.50 (1.18-1.91)**
Family Medicine	44	45.64	0.74 (0.55-1.01)	1.07 (0.76-1.50)	1.02 (0.73-1.43)
Tuberculosis Specialist	438	71.97	1.17 (1.04-1.32)*	1.12 (0.96-1.30)	1.09 (0.94-1.26)
General Medicine	271	65.50	1.07 (0.93-1.23)	1.15 (0.98-1.34)	1.21 (1.03-1.42)*
Other	139	47.88	0.81 (0.67-0.97)*	0.91 (0.74-1.11)	0.95 (0.77-1.16)

†Chi-square test, t-test and Cox proportional hazards regression
Mode 1 adjusted for patient characteristics , physician and practice characteristics, P4P participation and Charlson comorbidity index score (CCI) ††Mode 2 adjusted for characteristics , physician and practice characteristics, P4P participation and baseline comorbidities

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Rate, per 1000 person years

We further explored the influence of mood disorder on TB patients' mortality. Table 4.7 shows mortality rates for TB patients with mood disorder and associated risk factors. Using the multivariable Cox proportional hazards regression model, we found an increased risk of mortality in TB patients with mood disorder patients with the following characteristics:

1. Older age: TB patients who were older than 65 years of age had significantly higher risk of death regardless of mood disorder status (HR=3.82, 95% CI=2.28–6.42, P < 0.001; HR=6.60, 95% CI=5.19–8.38, P< 0.001). There was a trend of higher risk of death with increased age.

2. Male: both men with and without mood disorder had a higher risk of death than women (HR=1.68, 95% CI=1.35–2.09, P< 0.001; HR=1.29, 95% CI=1.13–1.48, P< 0.001).

3. Lower income: lower income patients had higher mortality rates in both mood disorder and non-mood disorder groups. (HR= 1.80, 95% CI = 1.22–2.66, P< 0.01; HR= 1.55, 95% CI = 1.27–1.90, P< 0.001).

4. Disability: TB patients with a disability had higher risk of death than TB patients without a disability in both mood disorder and non-mood disorder groups (HR = 1.44, 95% CI = 1.11–1.88, P< 0.01; HR = 1.41, 95% CI = 1.19–1.67, P< 0.01).

5. Commodity level: patients with higher the CCI score had a higher risk of mortality.

6. Gender of physician: male doctors had patients with higher mortality rates than female doctors in the non-mood disorder group .

7. Specialty of physician: Specialized infectious disease physicians and general medicine physician had patients with higher mortality rates than other specialties.

Table 4.7 The hazard ratio and 95% CI for all-cause mortality and associated risk factors in Cox proportional hazard regression (2002 - 2010)

	TB patients with mood disorder				TB patients without mood disorder			
	N	%	Crude HR (95% CI)	Model	N	%	Crude HR (95% CI)	Model
P4P								
No	225	67.81	1.00	1.00	788	58.15	1.00	1.00
Yes	151	81.06	1.14 (0.93-1.40)	0.97 (0.78-1.22)	444	69.16	1.10 (0.98-1.24)	0.93 (0.81-1.06)
All	376	72.57			1232	61.69		
Patient characteristics								
Age, year								
< 45	16	16.47	1.00	1.00	81	10.76	1.00	1.00
45-64	65	37.82	2.26 (1.31-3.90)**	1.83 (1.05-3.18)*	222	36.30	3.34 (2.59-4.31)***	2.55 (1.97-3.31)***
>= 65	295	118.44	6.86 (4.14-11.3)***	3.82 (2.28-6.42)***	929	146.83	12.6 (10.1-15.9)***	6.60 (5.19-8.38)***
Gender (male vs. female)								
Female	120	52.36	1.00	1.00	302	42.36	1.00	1.00
Male	256	88.61	1.68 (1.35-2.09)***	1.25 (0.99-1.57)	930	72.42	1.68 (1.48-1.91)***	1.29 (1.13-1.48)***
Insurance premium (NT$)								
< 15,000	155	107.19	3.47 (2.40-5.00)***	1.80 (1.22-2.66)**	496	78.10	2.58 (2.13-3.14)***	1.55 (1.27-1.90)***
15,000-19,999	186	72.58	2.36 (1.64-3.38)***	1.66 (1.14-2.42)**	608	65.72	2.19 (1.81-2.65)***	1.26 (1.03-1.54)*
>= 20,000	35	29.86	1.00	1.00	128	29.31	1.00	1.00
Urbanization								
High	184	67.48	1.00	--	553	53.01	1.00	1.00
Low	192	78.23	1.15 (0.94-1.41)	--	679	71.19	1.33 (1.18-1.48)***	1.00 (0.88-1.13)
Disability								
No	304	65.80	1.00	1.00	1066	56.27	1.00	1.00
Yes	72	128.30	1.89 (1.46-2.45)***	1.44 (1.11-1.88)**	166	161.81	2.67 (2.27-3.15)***	1.41 (1.19-1.67)***
Charlson comorbidity index score								
0	94	30.38	1.00	1.00	393	26.29	1.00	1.00
1	81	87.03	2.81 (2.08-3.78)***	2.00 (1.47-2.72)***	258	105.16	3.84 (3.28-4.49)***	2.22 (1.89-2.62)***
2	76	115.20	3.72 (2.75-5.04)***	2.60 (1.91-3.55)***	213	166.14	5.89 (4.98-6.96)***	3.13 (2.63-3.72)***
3+	125	251.91	7.73 (5.90-10.1)***	4.86 (3.66-6.46)***	368	286.55	9.52 (8.24-11.0)***	4.68 (4.00-5.47)***
Hospital characteristics								
Hospital level								
Medical center	141	76.35	1.00	1.00	453	62.57	1.00	1.00
District hospital	125	77.06	0.99 (0.78-1.26)	1.06 (0.83-1.36)	398	63.04	0.99 (0.86-1.13)	1.10 (0.94-1.27)
Regional hospital	82	72.47	0.94 (0.72-1.24)	0.88 (0.67-1.16)	306	73.09	1.16 (1.00-1.34)*	1.14 (0.96-1.36)

Others	28	48.22	0.64 (0.43-0.97)*	0.68 (0.45-1.03)	75	33.62	0.55 (0.43-0.70)***	0.91 (0.57-1.45)
Hospital ownership								
Public	22	47.67	1.00	--	56	32.43	1.00	1.00
Private religious	215	79.53	1.14 (0.92-1.42)	--	620	56.86	0.44 (0.34-0.58)***	0.88 (0.77-1.00)
Other	139	68.95	0.70 (0.45-1.10)	--	566	75.76	0.76 (0.68-0.85)***	0.67 (0.41-1.11)
Geographic location								
Taipei	79	62.42	1.00	--	253	51.25	1.00	1.00
Northern	35	56.92	0.90 (0.60-1.34)	--	126	4838	0.91 (0.74-1.13)	1.02 (0.81-1.28)
Central	93	80.49	1.27 (0.94-1.71)	--	233	63.09	1.19 (0.99-1.42)	1.09 (0.89-1.33)
Southern	72	86.95	1.36 (0.99-1.87)	--	279	88.15	1.66 (1.40-1.97)***	1.18 (0.96-1.45)
Kao-Ping	81	83.55	1.31 (0.96-1.78)	--	273	62.89	1.20 (1.01-1.43)*	1.11 (0.92-1.33)
Eastern	16	46.06	0.75 (0.44-1.28)	--	68	55.27	1.07 (0.82-1.39)	1.17 (0.88-1.67)
Physician characteristics								
Age, year								
< 35	64	93.12	1.00	--	172	58.56	1.00	1.00
35-64	311	70.24	0.76 (0.58-1.00)	--	1054	62.95	1.08 (0.92-1.27)	1.15 (0.97-1.35)
>=65	1	15.21	0.17 (0.02-1.25)	--	6	20.85	0.38 (0.17-0.86)*	0.70 (0.30-1.62)
Gender								
Female	15	48.04	1.00	--	41	34.41	1.00	1.00
Male	359	73.83	1.53 (0.91-2.57)	--	1188	63.30	1.85 (1.35-2.52)***	1.47 (1.07-2.03)*
Specialty								
Chest Medicine	162	77.4	1.00	--	480	59.38	1.00	1.00
Infectious Disease	17	91.25	1.17 (0.71-1.92)	--	57	81.57	1.35 (1.02-1.77)*	1.41 (1.07-1.87)*
Family Medicine	7	35.98	0.48 (0.22-1.02)	--	37	48.09	0.83 (0.60-1.16)	1.30 (0.89-1.90)
Tuberculosis Specialist	100	76.98	1.01 (0.78-1.29)	--	338	70.61	1.23 (1.07-1.41)**	1.14 (0.96-1.36)
General Medicine	58	67.00	0.89 (0.66-1.19)	--	213	56.10	1.13 (0.96-1.32)	1.26 (1.05-1.51)*
Other	32	58.89	0.79 (0.54-1.16)	--	107	45.34	0.82 (0.66-1.01)	1.03 (0.82-1.30)

Rate, per 1000 person-years; † Cox proportional hazards regression

†Mode adjusted for patient characteristics, physician and practice characteristics, P4P participation and Charlson comorbidity index score (CCI) * p< 0.05, ** p < 0.01, *** p < 0.001.

Rate, per 1000 person years

4.3 Study aim 3:

To achieve research **aim 3**) to examine the impact of P4P effect on TB treatment default and TB patients' mortality. the research questions and hypotheses are:

Research question 5: Does P4P with the TB program improve TB treatment default rate among TB with mood disorder patients ?

Hypothesis 5*:* TB patients with mood disorder enrolled in the P4P program have a higher default rate than those patients who are not enrolled in the P4P program in Taiwan.

Results:

The participation condition of P4P on TB program

The patient characteristics of P4P on TB participants

Table 4.8 lists comparisons of TB patients' characteristics and health status between P4P and Non-P4P groups by mood disorder status. A total of 5,327 tuberculosis patients were included in this study. Of these patients, 1140 patients had a mood disorder and 4187 TB patients did not have a mood disorder. In the mood disorder group, 460 were P4P enrollees (40.3%). The non-mood disorder group had less P4P participation rate (36.2%).

Age influences intention to participate in the P4P program ($P < 0.0001$). The mean age of TB patients in the mood disorder group was 64.8 years old, which was older than the age of TB patients in the non-mood disorder group (57.9 years old). Patients over 65 years of age accounted for more than half of the mood disorder patients (58%). In both groups, the majority of participants were older ($>$ 65 years), and were more likely to participate P4P on TB program.

In terms of gender, there were more male P4P participants than female. Males without a mood disorder were more likely to participate in the P4P program than females

(P< 0.0001). The insurance premium and urbanization factors had no significant effect on the patients' intention to participate in P4P.

More patients in the mood disorder group had a disability (13%) than patients in the non-mood disorder group (6.99%). In both groups, most of P4P participants had no comorbidity, especially in the non-mood disorder group. Patients with no comorbidity (Charlson comorbidity index score CCI=0) were more likely to enroll in the P4P on TB program (P< 0.0001).

Table 4.8 Comparison of TB patients' characteristics and health status between P4P and Non-P4P by mood disorder

	TB patients with mood disorder N=1140					TB patients without mood disorder N=4187				
	Non-P4P N=680		P4P N=460			Non-P4P N=2671		P4P N=1516		
	n	%	n	%	p-value	n	%	n	%	p-value
Patient characteristics										
Age, year					0.20					<0.0001
<45	107	15.7	63	13.7		906	33.9	425	28.0	
45-65	215	31.6	130	28.3		745	27.9	413	27.2	
>65	358	52.7	267	58.0		1020	38.2	678	44.7	
Means (SD)	63.0	(16.8)	64.8	(15.7)	0.07	54.5	(21.7)	57.9	(20.2)	<0.0001
Gender					0.07					<0.0001
Female	310	45.6	185	40.2		967	36.2	452	29.8	
Male	370	54.4	275	59.8		1704	63.8	1064	70.2	
Insurance premium					0.10					0.54
< 15,000	214	31.5	130	28.3		911	34.1	494	32.6	
NT$ 15,000-19,999	326	47.9	250	54.4		1235	46.2	726	47.9	
>=NT$ 20,000	140	20.6	80	17.4		525	19.7	296	19.5	
Urbanization					0.21					0.29
High	360	52.9	226	49.1		1381	51.7	758	50.0	
Low	320	47.1	234	50.9		1290	48.3	758	50.0	
Disability	89	13.1	60	13.0	0.98	190	7.11	106	6.99	0.88
Charlson comorbidity index score					0.006					<0.0001
0	372	54.7	218	47.4		1829	68.5	914	60.3	
1	107	15.7	108	23.5		333	12.5	245	16.2	
2	99	14.6	59	12.8		217	8.12	153	10.1	
3+	102	15.0	75	16.3		292	10.9	204	13.5	

Chi-square test, t-test
* p<0.05, ** p<0.01, ***p<0.001

The physician and health care facility characteristics of P4P on TB participants

Hospital characteristics

Table 4.9 presents the distribution of physician and health care facility characteristics for patient P4P participation. Hospitals have a significantly different P4P participation level (P< 0.0001). The majority of participants were from district level hospitals (44.5%) and medical center level hospitals (36.5%). District level hospitals were the main health care provider for TB patients. Private hospitals were also more likely to participate in the P4P program (59.2%, P< 0.0001). The distribution of P4P participation by hospital geographic location was fairly average. But central Taiwan had a higher P4P participation rate than other areas, and the eastern Taiwan had lower participation.

Physician characteristics

The majority of physicians providing care for the TB patients were aged 35 to 64 years (85%) and male (93%). Physicians' specialty had a significant effect on P4P participation (P< 0.0001). Physicians with a specialty in chest medicine were more likely to have patients to enrolled in the P4P program.

Table 4.9 Comparison the TB patients' hospital and physician characteristics between P4P and non-P4P by mood disorder

	TB patients with mental disorder N=1140					TB patients without mental disorder N=4187				
	Non-P4P N=680		P4P N=460			Non-P4P N=2671		P4P N=1516		
	n	%	n	%	p-value	n	%	n	%	p-value
Hospital characteristics										
Hospital level					<0.0001					<0.0001
Medical center	333	34.3	168	36.5		948	35.5	554	36.5	
District hospital	171	25.2	207	45.0		687	25.7	674	44.5	
Regional hospital	180	26.5	69	15.0		701	26.2	210	13.9	
Others	96	14.1	16	3.48		335	12.5	78	5.15	
Hospital ownership					<0.0001					<0.0001
Public	254	37.4	185	40.2		995	37.3	616	40.6	
Private religious	349	51.3	262	57.0		1415	53.0	836	55.2	
Other private	77	11.3	13	2.83		261	9.77	64	4.22	
Geographic location					0.045					<0.0001
Taipei	158	23.2	103	22.4		616	23.1	359	23.7	
Northern	87	12.8	43	9.35		344	12.9	201	13.3	
Central	137	20.2	121	26.3		390	14.6	404	26.7	
Southern	115	16.9	79	17.2		471	17.6	246	16.2	
Kao-Ping	147	21.6	81	17.6		691	25.9	223	14.7	
Eastern	36	5.29	33	7.17		159	5.95	83	5.47	
Physician characteristics										
Age, year					0.40					0.23
< 35	94	13.8	67	14.6		412	15.4	205	13.5	
35-64	578	85.0	391	85.0		2228	83.4	1295	85.4	
>= 65	8	1.18	2	0.43		31	1.16	16	1.06	
Gender					0.08					0.04
Female=2	32	4.73	33	7.17		139	5.21	103	6.79	
Male=1	645	95.3	427	92.8		2528	94.8	1413	93.2	
Specialty					<0.0001					<0.0001
Chest Medicine	206	30.3	281	61.1		771	28.9	986	65.0	
Infectious Disease	13	1.91	33	7.17		86	3.22	79	5.21	
Family Medicine	38	5.59	2	0.43		147	5.50	10	0.66	
Tuberculosis Specialist	218	32.1	72	15.7		812	30.4	194	12.8	
General Medicine	119	17.5	57	12.4		481	18.0	192	12.7	
Other	86	12.7	15	3.25		374	14.0	55	3.63	

Chi-square test, Fisher's exact test and t-test
* p<0.05, ** p<0.01, ***p<0.001

The influence of P4P participation on patient's default

From Table 4.3, patients enrolled in P4P on TB programs had significantly lower default rates in both those with and without mood disorder (OR = 0.20, 95% CI = 0.15–0.26, P< 0.001 in the mood disorder group; OR = 0.16, 95% CI = 0.14–0.19, P< 0.001 in non-mood disorder group). Although both groups had a decreased default rate from TB treatment after P4P participation, comparing the total default rate between mood disorder and non-mood disorder groups shows that the default rate of patients with mood disorder is still higher than that of patients without mood disorder.. In the Table 4.4, we examined the influence of P4P participation on patient's default among the mood disorder and non-mood disorder group. We stratified these two groups by patient, hospital and physician characteristics. Logistic regression was used to examine the effect of P4P on TB program. TB treatment defaults were significantly decreased in P4P participants based on patient's age, gender, income status, and comorbidity levels in both patients with or without mood disorder.

Research question 6: Does P4P with TB program improve mortality among TB with mood disorder patients.

Hypothesis 6: TB patients with mood disorder enrolled in the P4P program will have a lower mortality rate than those patients who are not enrolled in the P4P program in Taiwan.

Results:

Mortality of P4P on TB patients with mood disorder

Table 4.10 shows that P4P had no significant effect on mortality in both mood disorder status groups.

Table 4.10 Hazard ratio and 95% CI for P4P effect on mortality stratified by patient, hospital, and physician characteristics using multivariable Cox proportional hazard regression

	TB patients with mood disorder					TB patients without mood disorder				
	Non-P4P		P4P			Non-P4P		P4P		
	n	%	n	%	Model	n	%	n	%	Model
Patient characteristics										
Age, year										
< 45	9	13.73	7	22.13	1.94 (0.62-6.07)	52	9.72	29	13.32	1.30 (0.78-2.19)
45-64	40	35.06	25	43.27	0.87 (0.51-1.48)	143	33.96	79	41.47	1.17 (0.85-1.60)
>= 65	176	115.65	119	122.83	0.93 (0.72-1.19)	593	148.63	336	143.77	0.86 (0.74-1.01)
Gender (male vs. female)										
Female	67	43.38	53	70.91	1.16 (0.79-1.72)	215	42.43	87	42.20	0.77 (0.58-1.01)
Male	158	89.09	98	87.86	0.87 (0.66-1.14)	573	67.55	357	81.92	0.98 (0.84-1.15)
Insurance premium (NT$)										
< 15,000	95	99.60	60	121.90	1.12 (0.79-1.56)	319	72.48	177	90.80	0.97 (0.79-1.20)
15,000-19,999	106	67.72	80	80.19	0.90 (0.65-1.25)	387	62.65	221	71.89	0.94 (0.78-1.14)
>= 20,000	24	30.04	11	29.48	0.68 (0.31-1.50)	82	27.59	46	32.95	0.75 (0.49-1.14)
Urbanization										
High	116	65.65	68	70.85	0.92 (0.67-1.26)	365	51.03	188	57.33	0.87 (0.71-1.07)
Low	109	70.27	83	91.90	0.96 (0.70-1.33)	423	66.13	256	81.52	1.00 (0.84-1.20)
Disability										
No	179	60.30	125	75.69	1.03 (0.80-1.31)	679	52.74	387	63.75	0.95 (0.82-1.09)
Yes	46	131.52	26	122.98	0.69 (0.40-1.16)	109	161.02	57	163.34	0.80 (0.53-1.19)
Charlson comorbidity index score										
0	58	27.67	36	36.06	1.00 (0.64-1.55)	266	25.19	127	28.94	1.07 (0.84-1.36)
1	45	89.07	36	84.60	0.82 (0.51-1.32)	164	114.08	94	92.53	0.78 (0.59-1.04)
2	49	115.47	27	114.72	1.05 (0.63-1.74)	125	151.86	88	191.74	1.16 (0.84-1.60)
3+	73	249.59	52	255.24	0.98 (0.66-1.46)	233	320.10	135	242.65	0.76 (0.59-0.97)*
Hospital characteristics										
Hospital level										
Medical center	86	73.52	55	81.25	1.04 (0.73-1.47)	284	56.89	169	75.20	1.00 (0.79-1.26)
District hospital	53	66.32	72	87.49	0.87 (0.60-1.28)	202	59.35	196	67.36	0.89 (0.71-1.11)
Regional hospital	64	76.63	18	60.74	0.93 (0.55-1.58)	237	71.87	69	77.63	0.87 (0.66-1.15)
Others	22	42.81	6	89.89	1.86 (0.70-4.95)	65	35.00	10	26.77	0.86 (0.37-2.00)
Hospital ownership										
Public	92	76.12	47	58.21	0.86 (0.58-1.27)	92	76.12	196	75.89	0.80 (0.66-0.99)*
Private religious	115	67.61	100	99.76	1.05 (0.79-1.40)	380	67.61	240	68.10	1.06 (0.88-1.27)
Other	18	44.07	4	75.39	1.59 (0.47-5.33)	18	44.07	8	75.39	0.68 (0.23-2.03)

Geographic location										
Taipei	53	64.06	26	59.31	0.88 (0.53-1.45)	164	48.06	89	58.39	0.93 (0.89-1.24)
Northern	21	47.63	14	80.45	1.12 (0.43-2.91)	87	51.45	39	42.69	0.63 (0.38-1.07)
Central	46	70.86	47	92.83	1.07 (0.69-1.66)	87	43.15	146	87.07	1.17 (0.85-1.61)
Southern	50	98.09	22	69.12	0.73 (0.40-1.33)	199	94.06	80	76.25	0.75 (0.56-0.99)*
Kao-Ping	49	72.62	32	108.58	1.64 (0.95-2.80)	201	57.94	72	82.60	1.06 (0.78-1.43)
Eastern	6	27.76	10	76.23	1.38 (0.36-5.38)	50	59.06	18	46.91	0.99 (0.49-2.02)
Physician characteristics										
Age, year										
< 35	35	80.27	29	11.543	1.08 (0.62-1.89)	111	52.60	61	73.76	1.32 (0.91-1.92)
35-64	189	66.79	122	76.34	0.97 (0.76-1.24)	672	59.73	382	69.54	0.91 (0.79-1.05)
>=65	1	19.13	0	0.00	--	5	26.53	1	10.07	--
Gender										
Female	7	43.82	8	52.46	0.71 (0.19-2.60)	23	31.34	18	39.35	0.61 (0.22-1.69)
Male	216	68.52	143	83.61	1.00 (0.80-1.26)	762	59.51	426	71.45	0.95 (0.83-1.08)
Specialty										
Chest Medicine	64	66.33	98	86.95	0.85 (0.61-1.19)	200	51.81	280	66.31	0.96 (0.79-1.18)
Infectious Disease	4	59.29	13	109.39	0.46 (0.12-1.80)	31	77.39	26	87.19	1.36 (0.64-2.89)
Family Medicine	6	31.93	1	150.74	--	33	45.53	4	89.66	1.54 (0.41-5.70)
Tuberculosis Specialist	84	83.67	16	54.23	0.76 (0.43-1.35)	278	69.93	60	73.96	0.76 (0.57-1.02)
General Medicine	38	61.48	20	80.76	1.15 (0.65-2.04)	151	61.44	62	76.14	1.08 (0.78-1.51)
Other	29	60.95	3	44.37	1.04 (0.28-3.80)	95	44.57	12	52.52	0.85 (0.44-1.64)

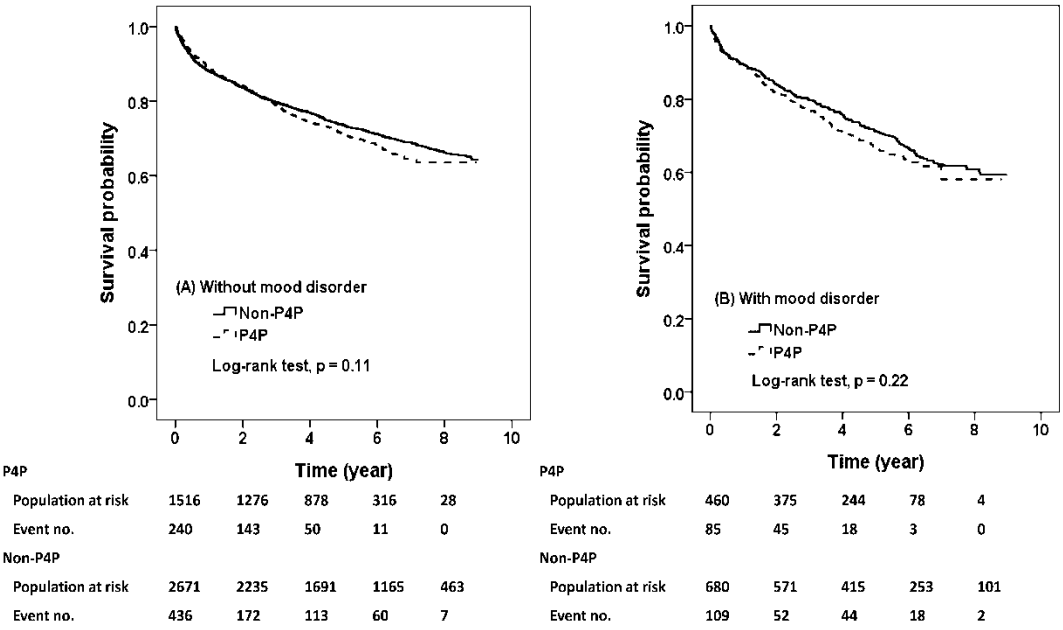
Rate, per 1000 person-years

† Cox proportional hazards regression

†Mode adjusted for patient characteristics , physician and practice characteristics, P4P participation and Charlson comorbidity index score (CCI)

*p< 0.05, **p < 0.01, ***p < 0.001.

Using Kaplan-Meier for analyzing survival probability between TB patients with and without P4P by mood, we found that among both mood disorder and non-disorder TB patients, P4P program had no impact on survival (non-mood disorder log rank test p= 0.11 ($p > 0.05$); mood disorder log rank test p= 0.22 ($p > 0.05$)) (Fig. 4.2). From the results of Table 4.8, we stratified factors of mortality by patient, hospital, and physician characteristics. This also showed that P4P had no significant impact on mortality among TB with or without mood disorder.



P4P					
Population at risk	1516	1276	878	316	28
Event no.	240	143	50	11	0
Non-P4P					
Population at risk	2671	2235	1691	1165	463
Event no.	436	172	113	60	7

P4P					
Population at risk	460	375	244	78	4
Event no.	85	45	18	3	0
Non-P4P					
Population at risk	680	571	415	253	101
Event no.	109	52	44	18	2

Figure 4.3 Survival probability between TB patients with and without P4P in Kaplan-Meier analysis by mood disorder status

5. CHAPTER FIVE: DISCUSSION AND IMPLICATIONS

5.1 Summary of findings

In summary, our epidemiological study provides an exploration of the prevalence of mood disorder among TB patients and the relationship between risk of mood disorder and TB treatment outcome. We estimated the prevalence of mood disorder among TB patients to be 12.6% in Taiwan, which was higher than the prevalence in the general population. Anxiety was the leading mood disorder (83.4%). Elderly, females, high-income patients, disabled patients, and patients with a high CCI score had a significantly higher chance of having a mood disorder. Patients with a mood disorder were less likely to participate in the P4P program and had a higher default rate than patients without a mood disorder. Risk factors for patients' default are having a mood disorder and being female. Regional level hospitals and family medicine specialties had the highest default rate. Patients with a mood disorder, elderly patients, males, lower-income patients, patients with a disability, and patients with a high CCI had significantly higher risk of increasing mortality. P4P on TB program can decrease the default rate had no significant influence on all-cause mortality.

5.2 Discussion:

5.2.1 Study aim 1:

Research question 1: What is the prevalence of mood disorder among TB patients in Taiwan?

Hypothesis 1: The prevalence of mood disorder is higher in TB patients than in the general population in Taiwan.

Discussion: The lifetime prevalence of mood disorder in patients with chronic disease is from 8.9% to 12.9% (Bernstein, 2004; Cassem, 1990). Previous studies found that the prevalence of mood disorder in patients with TB ranges from 11.3-80.2% (A. Sweetland, Oquendo, Wickramaratne, Weissman, & Wainberg, 2014). The estimated prevalence of mood disorder ranged from 13.3%-52.2% in Peru (Vega, et al., 2004), 22%-72% in Pakistan (Aamir & Aisha, 2010; Mohammed O Husain, 2008), 7%-10% in India (Rajeswari, 2005), 19%-25.6% in Turkey, and 21.1%-56.1% in China (Pan, et al., 2006). The wide range in these studies is attributed to the different scales used and the fact that most of the studies had a small sample size.

In our study, psychiatric diagnosis, in particular, is made by qualified psychiatrists after professional clinical interviews. This is more reliable, considering the differential mood conditions of patients. Additionally, our datasets from the NHIRD had a large sample size and could be generalized. From our results, the prevalence of mood disorder in the general population in Taiwan was 12.6%, which is close to that in the UK and the United States. Since tuberculosis is a disease that impacts both the individual and society, patients' first react to the diagnosis with tension/anxiety (30%), loss of interest/depression (26%), denial (6%) and suicidal thoughts (9%) (Rajeswari, 2005; Shen et al., 2014; U Eram, 2006). Our study estimated that 26.8% of TB patients in Taiwan have a mood disorder, which was two times higher than the prevalence of mood disorder in the general population. It was not surprising that anxiety (83.4%) was the most common mood disorder. These emotional problems may be explained by feelings of stigma, discrimination, and social isolation associated with TB. Therefore, individuals diagnosed with TB are more likely to be psychological distressed than the general

population. Our results indicate high mood disorder morbidity in TB patients, as consistent with other studies.

Research question 2: Among TB patients, what patient characteristics are associated with the presence of mood disorder in Taiwan?

Hypothesis 2 : Patient's age, gender, socio-economic status, location of residence, disease severity, and other co-morbidities are associated with the presence of mood disorder among TB patients.

Discussion: A previous study examined the association between burnout, depression, anxiety, and inflammation as risk factors for cardiovascular disease (Chung et al., 2014). Researchers used C-reactive protein as a specific protein biomarkers for measuring inflammation. They discovered that there was an association between burnout and inflammation in women but not in men. Depression, not burnout or anxiety, produced similar elevated levels of inflammation in men (Suarez, 2004; Toker, Shirom, Shapira, Berliner, & Melamed, 2005). When women are diagnosed with TB, they may experience loss of intimacy with their husbands, damage relations with children and relatives, and be avoided by neighbors or colleagues. People who perceived stigma may have a low self-image and be socially isolated, which may predispose them to common mental disorders (Deribew et al., 2010). Thus, these physical and psycho-social risk factors make women more prone to mood disorders than men.

Implication: It is important for primary care physicians treating patients with TB to be mindful of the clinical manifestations of mood conditions. Early appropriate psychiatric referral might identify patients with mood disorders. This may provide appropriate psychosocial support and medical aids to improve their quality of life.

5.2.2.Study aim 2:

Research question 3: Do TB patients with mood disorder have the same rate of treatment default rate as TB patients without mood disorder in Taiwan?

Hypothesis 3: TB patients with mood disorder have a higher default rate than TB patients without mood disorder in Taiwan.

Discussion:

Under the national guidelines for TB diagnosis and treatment by the Taiwan CDC (TCDC, 2015), first line medications include rifampin, isoniazid, pyrazinamide and ethambutol. The suggested treatment duration is six months in general, and nine to twelve months for retreatment or complex patients. It is not easy for patients to adherence to this long term treatment-taking behavior. It had been reported that up to half of all of patients with TB do not complete treatment (Cuneo & Snider, 1989; Menzies, Rocher, & Vissandjee, 1993). Unfortunately, after tuberculosis onset, emotional disturbance will also appear because of psychological issues such as stigma, isolation, sense of little social support, helplessness, and other psychological reactions to the disclosure of the diagnosis as well as medication side effects, all of which adversely affect the treatment adherence. Based on our study results, patients with mood disorder were less likely to participate in the P4P program and had higher default rates than patients without mood disorder. Our study found that mood condition may play as a barrier to treatment adherence. This is consistent with previous research which suggests that mood disorder may contribute to TB prolonged infection, drug resistance, relapse, and death (Canaza et al., 2013; Volmink & Garner, 2007). In addition, our results show that no comorbidity patients were more

likely to participate in the P4P program, but the more comorbidities they have the less likely to default to TB treatment. This is possibly due to a fear of becoming more ill and having to strictly follow the physician's advice. In order to increase the positive treatment outcomes of tuberculosis patients, comorbidities must be firstly identified and treated.

Gender was an interesting factor in our study finding. Females were more likely to develop mood disorders, but less likely to participate in the P4P program, and had more interrupted treatment than male. Gender differences in treatment adherence is still divergent in many studies (Alobu, Oshi, Ukwaja, & Oshi, 2015; Johansson, Long, Diwan, & Winkvist, 1999; Y. H. Li, et al., 2010). Some studies debated that a female patient's role and responsibilities in the family could motivate them to adhere to treatment in order to recover and resume those duties (Khan, Walley, Witter, Shah, & Javeed, 2005; Krishnan et al., 2014; Y. H. Li, et al., 2010; SS Sarpal, NK Goel, D Kumar, & Janmeja, 2015; Wares, Singh, Acharya, & Dangi, 2003). Other studies found that responsibilities in the home, such as providing income and caring for children, also reduced the likelihood of treatment adherence for women (Greene, 2004). We believed that "gender" refers not only to the physiological differences between sexes but also to the variety of health seeking behaviors, expectations, and roles that exist within a social, economic, and cultural context (Y. Li et al., 2013). Logically both males and females are infected, progress to disease, and die due to tuberculosis. Also, males and females share many similar beliefs and attitudes about tuberculosis. However, there are considerable differences with regard to stigma and its social consequences. Not just the individuals but the whole family may also suffer from social stigma and its negative consequences, which make the female family members feel suffering. Previous research mentioned a

relationship between pregnancy and non-adherence to TB treatment (Fong, 2004). Female patients who were, or wanted to be, pregnant were less likely to adhere to treatment as they perceived the medication to be harmful. Two more studies also found that women diagnosed with TB during pregnancy are at increased risk for having low birth weight and small for gestational age infants (Jana, Barik, & Arora, 2010; Lin & Chen, 2010). Females feel guilt over the TB medication impact on their baby, which may cause them to be hesitant about continuing treatment. Moreover, Genital TB has shown to be cause of infertility (Hardy & Anderson, 2015). Physicians should be aware of the potential maternal and fetal adverse outcomes for women diagnosed with TB and practice more intensive monitoring during pregnancy.

Stigma may lead to delays for both sexes in seeking care, but more so for females if there are physical, geographical, and economic barriers to health care (Alobu, et al., 2015; Anderson de Cuevas et al., 2014; Balasubramanian et al., 2004; Chen et al., 2014; Ting et al., 2014). Although there has been increased advancements in gender equality, the social expectation of a female role is not only as a caregiver to the family and home, but also comes with the need to be working and sharing responsibilities of raising families.

Stigma may also make patients afraid to ask for support from their employer. Studies suggested that patients hide their disease for fear that employers may discover that they have TB, fear of obtaining sick leave for treatment and fear of losing work or dismissal (Greene, 2004; Johansson, Diwan, Huong, & Ahlberg, 1996; Johansson, et al., 1999). Several studies noted that, in some cultures, a man is perceived as superior to a woman, and thus men's health is prioritized. Women are expected to care for husbands

with TB but men are not expected to care for wives with TB. (Balasubramanian, et al., 2004; Chen, et al., 2014; Johansson, et al., 1996; Johansson, et al., 1999; Liam, Lim, Wong, & Tang, 1999; Sanou, Dembele, Theobald, & Macq, 2004; Ting, et al., 2014). This attitude is still prevalent in Taiwan, particularly in rural areas. Hence, empowering women and encouraging families to give them support is very important for women (WHO, 2015a). It may include emotional and financial support, and a temporary substitution for the female's caregiver role.

In Taiwan, the National Health Insurance (NHI) program was implemented in 1995. As a result, utilization and accessibility of health care services have greatly improved. The NHI is a compulsory universal health program that offers complete freedom of choice of health care providers and allows TB patients to seek free medical aid from any health care institution or any primary practitioner. In our study, higher default rate in patients was observed more often among family medicine doctors than in chest medicine doctors. This is likely due to the physicians' expertise with TB. Chest medicine doctors were more likely to recruit their patient to P4P on TB program. This is consistent with other research that shows that patients treated by pulmonologists appeared to have higher treatment success rate than those treated by non-pulmonologist physicians (Chung, et al., 2007). A pivotal factor may be the unfamiliarity of physicians with the treatment of TB. Patient with a more strict out-patient follow-up procedure and more scrupulous patient education programs will have better success in treatment. Training for care providers and the institution providing the care is an important factor that affects the quality of care.

For most patients, access to a health care facility depended on distance, available transportation, as well as their physical condition. Studies have noted that access to health care facilities was better in urban areas than rural areas (Johansson, et al., 1996; Liam, et al., 1999). In our study, district and regional level hospital had more P4P participation but regional hospitals had highest default. This may be explained by the fact that most of the lower level hospitals are located in rural areas. The referral system is insufficient, with relative lack of medical resources in rural areas, especially for patients with comorbidities.

5.2.3 Study aim 3

Research question 5: Does P4P with the TB program improve TB treatment default rate among TB with mood disorder patients ?

Hypothesis 5: TB patients with mood disorder enrolled in the P4P program have a higher default rate than those patients who are not enrolled in the P4P program in Taiwan.

Discussion:

The results of this study show that the P4P program has had a positive effect on outcome for TB patients. Patients in P4P on TB programs had significantly lower default in both with and without mood disorder TB patients. However, in Taiwan there are still a few hospitals that refused to participate this program. There are several reasons for this, and the incentives are different by stage of treatment. Hospitals must follow the P4P contract; whenever they enroll one hundred new TB cases, they must hire an extra case manager. This case manager coordinates with the patient, the hospital, the community, and the government's CDC. Cooperation between professionals in multidisciplinary teams tends to vary widely across hospitals. This extra work is costly but is not rewarded.

Therefore some hospitals, especially those in which multidisciplinary teams, are not well coordinated. They are also concerned that the P4P program on TB could reduce total payment for an enrolled patient if the patient does not complete the full care package per the treatment plan and reduce the bonus based on patient's TB treatment outcome such as negative sputum finding and chest X-ray. The treatment procedure is divided into 4 phases (each 3 months), and health care providers receive bonuses if they complete the uninterrupted case management procedure in each phase. Otherwise, the reimbursement switches to the standard non-bonus scheme afterward as a punishment. As compared to treat multiple drug resistant TB patients, this program pays a more generous bonus. Thus, hospitals are reluctant to take over the multiple drug resistant or complex cases to avoid increasing their cost. As a result, some hospitals prefer to retain the original payment scheme so as to reduce financial risk in the case of incomplete treatment or overuse of resources due to complications.

Implications: Many studies suggested that better TB treatment adherence resulted in better outcomes, and reduced burden of cost and drug resistance. Mood disorder is associated with poor adherence to medication in the treatment of TB. Screening and follow-up for mood disorders are recommended for TB patients, which could reduce the TB burden by increasing treatment adherence. In addition to medical treatment, mental health support for TB patients may also lead to improved treatment outcomes. The findings could help inform the development of patient-centered interventions and interventions to address barriers to treatment adherence. In order to increase positive treatment outcomes for TB patients with mental health conditions, comorbidities must be

firstly identified and treated. Health workers also need to better understand the effects of gender, age and social aspects of tuberculosis control.

Research question 4: Do TB patients with mood disorder have the same mortality as TB patients without mood disorder in Taiwan?

Hypothesis 4: TB patients with mood disorder have a higher mortality rate than TB patients without mood disorder in Taiwan.

Research question 6: Does P4P with TB programs improve the effectiveness of TB treatment among TB patients with mood disorders in terms of TB mortality.

Hypothesis 6: TB patients with mood disorder enrolled in the P4P program will have a lower mortality rate than those patients who are not enrolled in the program in Taiwan.

Discussion:

Mortality studies have contributed considerably as indicators of health care quality for inpatient and outpatient services. Our study investigated all-cause mortality among TB patients with and without mood disorder from the year 2002 to 2010 (a total of nine years of follow-up time). We found that TB patients with mood disorder had an 1.8-fold increased risk of all-cause mortality than patients without mood disorder. Mood disorder may contribute to negative TB outcomes in several ways. TB may increase risk of depression or worsen the depression symptoms due to increased symptom burden, increased in inflammatory factors, and decreased quality of life (Suarez, 2004; Toker, et al., 2005). Comorbid mood disorder has been found to impair the ability to perform self-care activities, reduce total life expectancy significantly, and increase overall mortality by

almost two-fold (Cuijpers & Smit, 2002; Reynolds, Haley, & Kozlenko, 2008). Our results are consistent with previous studies.

In our study, the mortality rate of TB patients in Taiwan increased with age. TB prevention in the oldest age group (⩾65 years) is more difficult due to comorbidities and other factors. A recent study found that elderly patients with chronic kidney disease, stroke, or chronic liver disease as a comorbidity were more likely to die from TB-specific causes (Chu, Wu, Lo, Yang, & Chou, 2015). The increase in longevity of the general population of Taiwan has led to a larger pool of individuals with increased susceptibility to a flare-up of latent tuberculosis. It has been assumed that the high rate of tuberculosis in the elderly could also be due to the high rate of infection experienced in childhood or as young adults (Frost, 1995). After World War II, BCG vaccine was introduced to Taiwan in 1951. Fortunately, the youngest group (age <45) had received BCG vaccines in their childhood.

In previous research, aging has been revealed to be associated with progressive immune dysregulation. The most important finding is a progressive decrease in the CD8+ T-cells (Davies, 1999; Lesourd, 2004). This degeneration of the immune system makes the elderly more prone to infection or disease relapse. Cause of death in our study varied. Since most of the TB patients were of old age and many patients' had poor and complicated physical conditions, there was a combination of a lot of serious comorbidities. Patients in the end stage of cancer, or on the verge of dying or cachexia, have lower immune system function which may cause past TB to be reactive. Therefore it is difficult to distinguish whether the death was related to TB or other comorbidities. As most TB incidence among the elderly is due to reactivation of old TB, death certificates

were incorrect in most of these cases, with old TB being listed as a contributing factor and not directly related to the cause of death. Sometimes people died for TB while having had other diseases, and the Death Registry may not code TB as the major cause of death. Therefore, the true number of TB deaths was possibly higher than we estimate. Thus, further research may consider using primary medical chart review to explore this issue.

In addition, socio-economically deprived people in Taiwan are a vulnerable group. Poor older patients are less well-off than younger patients Poverty and poor nutritional status, in addition to mood disorder, are risk factors for high rates of tuberculosis in the elderly. Old age is significantly associated with treatment failure and death.

Implication: Reduction in mortality is possible through various interventions such as improved nutrition, urbanization, vaccination, medical treatment, and health education.

5.3 Policy Implications

This study explored the prevalence and the impact of mood disorder on TB patients, as well as how the P4P on TB program plays a role in the treatment of comorbid TB and mood disorder compared to only TB. From the results of this study, we provided policymakers with information on the impact of comorbid mood disorder and TB and the role of the incentive program. The government might decide whether or not to reinforce or improve the current TB control plan. Policies that may mitigate the influence of mood disorder on TB are suggested in the next section.

5.3.1 Developing a mood screening tool for TB patients and constructing a mental status follow-up system in TB registry management files

Many mood screening tools have been used widely. They include: Hospital Anxiety and Depression scale (HADS), Beck Depression Inventory (BDI) and the Center for Epidemiological Studies Depression Scale (CES-D) for depression, Spielberger state-trait anxiety scale and State-Trait Anxiety Inventory for anxiety. Some screening tools have too many questionnaires may make patients feel frustrated and tired of answering them. The mood disorder screening tool should be tailored and designed especially for TB patients. This screening tool may include:

1).The Mood Disorder Questionnaires: questions about specific symptoms of mood disorder and anxiety, including how long the symptoms have been present.

2). Ask whether they have caused problems in social relationships or work.

3). Always ask about suicidal ideation.

4). Add open-ended and non-leading general questions about the symptoms of emotional distress. Let patients be free to express themselves and their emotional condition.

5). Interview patient's family or friends regarding emotional supports.

6). Listen to the patient's unprompted presenting complaints.

5.3.2 Recruitment of psychological professionals to the TB care team and reinforce the referral system

After initial pharmacotherapy and related clinical management, care should ideally be provided with a healthcare team that includes at least one other psychological professional in addition to the physician. While primary care physicians are treating patients with TB they need be mindful of the clinical manifestations of mood condition.

Early appropriate psychiatric referral might identify patients with mood disorder and provide appropriate psychosocial support and medical aids sooner.

In Taiwan, a TB case manager is usually a nurse who contacts people in the hospitals for TB-related matters. The BNHI requires hospitals reporting over one hundred TB cases a year to have TB case managers. Usually, they are senior nurses who receive additional training and education about TB control. They track patients' revisits, educate patients on health matters, update patients' information in the central database, and coordinate patient management with public health nurses and local health officials. Essentially, TB case managers are responsible for all TB related matters in the hospitals.

Case managers must be well trained for caring for patient's psychological conditions. Case managers may provide detailed psychological education, additional monitoring, and support. Monitoring involves active outreach and follow up of patients known to be severely ill, to ensure patients attend appointments and follow recommendations. Case managers involve the provision of robust psycho education, whose elements would include preparing the patient to become actively involved in self-management, identifying ways to collaborate most effectively with health providers, teaching key facts about bipolar disorder, teaching recognition of early signs of relapse, identifying a relapse drill, and learning a variety of key stress management techniques, including careful attention to sleep regulation and avoidance of medication misuse. The workload for case managers is very heavy. We recommend NHI Bureau provide more funds to recruit psychological professionals in care team.

5.3.3 Improvement of the mental care abilities and sensitivity to mood disorder among TB patients in all hospitals, particularly regional hospitals

The TB care providers need to have the capability to provide TB patients with more comprehensive care. Health departments should periodically hold TB education and training for healthcare providers.

In teaching health workers about TB control, we tend to concentrate on technical aspects, while there is a great need for better understanding of behavioral factors and for developing strategies, that take these into account. When we improve the care capabilities of hospitals, the whole setting such as work environment, equipment and facilities, communication, management and leadership must be taken into account simultaneously. This may include minimizing costs and unpleasantness related to clinic visits and increasing flexibility and patient autonomy.

5.3.4 Patient-centered approach

The "disease-oriented" care model in the past may not enough to satisfy patients' need. A patient-centered" approach is a better way to provide care for this unique group. For example, gender sensitive strategies need to be developed in order to solve problems and fit the patients' cultural background and special needs. Comprehensive services are of importance at all levels of the health system, in order to make them more accessible and affordable, for both men and women.

The strategies may involve elements of a healthcare system for effective care of TB with mood disorders patients, such as:

Self-management support: to empower vulnerable groups such as elderly, female, low socio-economic and disability groups, and prepare patients to manage their health and health care.

TB education in communities: to provide TB education and increase the visibility of TB programs in the community, which may increase knowledge and improve attitudes towards TB. This program may provide more information about the disease and treatment to patients and communities. We need to encourage communities to increase TB patients support from family, peers, and social networks.

Health system: to reconsider the delivery system design for TB patients, to reduce their waiting time, keep their privacy, and reduce their barriers of transportation to visit hospitals.

5.3.5 Empowering women for break barrier

In 2013, WHO reported an estimated 3.3 million women falling ill with TB. The vast majority of TB deaths are in the developing world where gender inequities are very common. TB among mothers is associated with a six-fold increase in prenatal deaths and a two-fold risk of premature birth and low birth-weight. We need to mobilize at global and national levels to assure gender-equitable access, including women friendly services to TB prevention, diagnosis, treatment care and support. TB, HIV, maternal, neonatal and child health programs, and primary care services should collaborate to maximize the entry points to TB care for women at all levels. We should integrate TB screening and investigation into reproductive health services, including family planning, antenatal and postnatal care in all settings.

5.3.6 TB Patient club and internet

Compared to patient clubs for other disease, it is rare to see TB patient clubs in our society. This is probably because of stigma and fear of discrimination or society's fixed impression of contagious disease. In this internet generation, we may use internet sites such as Face book or Line to form support groups. The internet has the advantages of keeping patient's privacy, breaking isolation and breaking the time, spatial and distance limitation. Patients could support each other in adhering to treatment, and to share information about the course of the disease and possible drug side effects through their treatment course. They also can clarify some misconceptions about the effects of medication to reduce the risk of patients becoming non-adherent when experiencing treatment side effects.

5.3.7 Law and legislation: anti-discrimination

TB patients' discrimination and exclusion are a long-standing social phenomenon. This social phenomenon is not reduced by social progress and civilization. In recent years, TB discrimination events are still been reported frequently. In 2007, a graduate student was denied admission by Guangzhou Institute of Geochemistry, because of his TB suspected laboratory results. Even by physician's guarantee that his condition was not contagious, the school still insisted on its decision. This was the first lawsuit against discrimination to protect TB patients' right to education in China (zjh, 2011). Taiwan also had the same issues. A college student was prohibited from presenting in her class because she was diagnosed TB.

Although TB can be spread to others, it is not as contagious as many airborne viral infections, such as measles and chicken pox. A single or a casual contact with an infectious person in a public place (such as subways, airplanes, movie theaters or on campus) usually does not cause the transmission of TB. The infectiousness of patients diminishes rapidly once effective treatment is initiated, as long as the patient adheres to the treatment regimen. Within two weeks of starting medication, the patients may become noninfectious. According our communicable Disease Prevention Law Article 16, any unit or individual shall not discriminate against patients with infectious diseases, pathogen carriers or suspected patients with infectious diseases. For patients with early stage or non-infectious tuberculosis, they still shall be entitled by the Constitution of basic human rights. TB patients should have the right to life, the right to learn, the right to work, the right of privacy, drug management rights, personal liberty, and the right to freedom of residence.

The government should reconsider whether the law has enough protection capabilities. Continuing examination of the legal basis and investigation of the actual practice are needed. It is necessary to educate people (including schools, communities, government agencies, and organizations), in order to change the public's negative stigma of TB, and to protect the basic human rights of patients.

5.4 Strengths and Limitations

This study may be subject to several limitations and threats. First, only TB patients in Taiwan are included in the study. The unique culture and healthcare system in Taiwan may limit the study results to be inapplicable to other geographical areas or other nations.

Second, the analysis was from claimed data that was definitely influenced by medical resource utilization behavior. For example, untreated patients were not included. Third, the outcome measures used in the study may be limited, encompassing only patient outcomes, and not representing all dimensions of the quality of care that TB patients receive. For example, the quality of diagnosis, additional support, and monitoring of TB patients by the participating hospitals in the P4P program are not evaluated and compared. In addition, rewards might largely depend on patient adherence to treatment plans as well as patient lifestyle. As patient lifestyle cannot be identified through claims data, it was not controlled for in this study. Moreover, the study may be subject to a bias that TB patients treated by the participating hospitals and non-participating hospitals may be different (for example, in terms of their disease severity and socio-economic status). Although I adjusted for many patient and hospital characteristics to control for these differences, there may be some unobservable confounders. For example, patients who are better in self-disease management may be more likely to look for better care and will be treated in the program-participating hospitals. However, I do not expect that this patient self-selection will be a serious threat to this study because the BHNI and participating hospitals did not promote this program in the general patient population. Most of the patients were therefore unaware of this P4P program. TB patients had no information to look for to be treated by these participating hospitals. Moreover, all TB treatment expenses were covered by the national health insurance with limited copayments, which might also reduce the possibility that patients with better socio-economic status were treated by participating and better equipped hospitals.

In spite of the limitations mentioned, there are strengths and new contributions

gained from this study. First, this study observes all TB patients in Taiwan, which provides a large study population and makes it possible to describe the co-morbidity TB and mood disorder, as well as to evaluate the impact of mood disorder on the TB treatment. Moreover, this study provides more information on the P4P on TB program in Taiwan. Though the program has been evaluated by a few studies that have shown its positive effects on TB treatment completion, default rate, and mortality, this study provides more information about whether this program also benefits TB patients with mood disorder, a group of patients that is more challenging treat. The study's results also shed light on the evaluation of a P4P program focused on a disease with a clear treatment course and outcome.

5.5 Future Research

Our results showed epidemiological information of the differences between men and women in prevalence of TB infections, prevalence of mood disorder among TB infection, rate of progression from infection to TB, and mortality. Yet, it is unclear why more males than females are diagnosed with tuberculosis. Research on gender and tuberculosis that combine biological and social factors within this field is insufficient. Sex-specific biological characteristics in tuberculosis patients have been a neglected area for research, and need to be acknowledged and explored in the future. Aging effects and psychosocial factors are complex. Whether and how these variables contain the causal relationship also need to be further examined.

From our study findings, the regional hospitals and below regional level hospitals had higher P4P participation rates than medical centers, but also had poor treatment

outcome. Whether their capacity is too limited to handle the extra work required by the program or whether a more generous bonus could improve their performance requires further investigation.

Furthermore, the NHI research dataset lacks patient's life style, weather, and environment factors. In recent years, air pollution has been noticed to negatively influence human's health, especially particulate matter having a diameter of less than 2.5 μm (PM2.5). This impact had been reported in Wuhan, China and in North Carolina, USA. (Chart-Asa & Gibson, 2015; Jakubiak-Lasocka, Lasocki, Siekmeier, & Chlopek, 2015; Liu, Skjetne, & Kobernus, 2013; X. Yang, Duan, Wang, Zhang, & Jiang, 2014). Taiwan is a small island but has high population density. The seasonal wind blows from the southwest of Taiwan during the summer monsoon and from the northeast in October to April. It brings numerous small particulate to Taiwan. Whether patient contact during the high peak of commuting times and overcrowding during festival and family gatherings will quicken spread TB and induce emotional stress, it is still unclear. Further research may focus on the association between pulmonary TB and outdoor air pollutants, seasonal variation, temperature, or long-term exposure to particulate matter (PM) 2.5 concentration.

5.6 Conclusion

Our findings indicated that mood disorder serves as a major barrier to treatment adherence. TB patients with mood disorder had significantly lower survival rates. P4P on TB program can decrease default but had no significant influence on all-cause mortality. Our results suggest that mental health evaluation and treatment should be regularly

incorporated in the management of TB patients. There is a need to provide adequate tools to the clinician to identify and manage these patients at this primary care level. Early appropriate psychiatric referral may identify patients with mood disorder. TB psychiatric co-morbidity must be first identified and treated. Managing coexisting psychiatric disorder can alter the course of TB. Providing family support is very important for women; this may include emotional and financial support, and a temporary substitute the female's caregiver role. Old age was significantly associated with treatment failure and death. Through various interventions such as improved nutrition, urbanization, vaccination, medical treatment and health education, TB mortality can be reduced.

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Appendix

Appendix A :

The rewards of P4P on TB program by stage of the TB treatment (TCDC 2002):

1) First stage (Identification of the disease and continuous medication for three months): The payments include medical care payment for the disease manager for the 1st stage (1,500 points) and a physician payment for 500 points. The total payment for this stage is 2,000 points.

2) Second stage (Continuous medication from 4th month to 6th month): Payments include medical care payment for the disease manager for the 2nd stage (1,500 points). If the cases are cured within 6 months, the case physicians can receive 1,000 points for the medical case payment.

3) Third stage (Continuous medication from 7th month to 9th month): The payments include the medical care payment for the disease manager for the 3rd stage (500 points). If the cases are cured within 9 months, the case physicians can get 1,000 points for the medical case payment.

4) Fourth stage (Continuous medication from 10th month to 12th month): Medical care payment for the disease manager is paid monthly (500 points). The case physician can receive 1,000 points when the cases are cured. If the cases are of multidrug-resistant tuberculosis, the hospital can declare a special fee for the case manager for 2,000 points, and the special case physicians can receive 1,000 points for providing medical care. After 13 months, the case manager will not get any more payments for medical care, except those with special cases (multidrug-resistant tuberculosis).

Appendix B:
Definitions of tuberculosis cases and treatment outcomes (World Health Organization, 2005)

A. Definitions of Tuberculosis Cases

Case of Tuberculosis: A case of TB which has been bacteriological confirmed, or has been diagnosed by a clinician.

Definite Case: Patient with positive culture for the *Mycobacterium tuberculosis* complex. In countries where culture is not routinely available a patient with two sputum smears positive for acid-fast bacilli (AFB+) is also considered a definite case.

Pulmonary Case: A case of TB disease involving the lung parenchyma.

Smear-Positive Pulmonary Case: At least two initial sputum smear examinations (direct smear microscopy) AFB+; or one sputum examination AFB+ and radiographic abnormalities consistent with active pulmonary tuberculosis as determined by a clinician; or one sputum specimen AFB+ and culture positive for *M. tuberculosis*.

Smear-negative Pulmonary Case: Pulmonary tuberculosis not meeting the above criteria for smear positive disease. Diagnostic criteria should include: at least three sputum smear examinations negative for AFB; and radiographic abnormalities consistent with active pulmonary TB; and no response to a course of broad-spectrum antibiotics; and decision by a clinician to treat with a full course of ant tuberculosis therapy; or positive culture but negative AFB sputum examinations.

Extra-pulmonary Case : Patient with tuberculosis of organs other than the lungs e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. Diagnosis should be based on one culture-positive specimen, or histological or strong clinical evidence consistent with active extra pulmonary disease, followed by a decision by a clinician to treat with a full course of anti-tuberculosis chemotherapy. Note: a patient diagnosed with both pulmonary and extra pulmonary tuberculosis should be classified as a case of pulmonary tuberculosis.

New Case: Patient who has never had treatment for tuberculosis, or who has taken anti-tuberculosis drugs for less than one month.

Relapse Case : Patient previously declared cured but with a new episode of bacteriologically positive (sputum smear or culture) tuberculosis.

Re-treatment Case: Patient previously treated for tuberculosis, undergoing treatment for a new episode of bacteriologically positive tuberculosis.

Appendix B:
Definitions of treatment outcomes (World Health Organization, 2005)

Cured: Initially smear-positive patient who was smear-negative in the last month of treatment, and on at least one previous occasion. **Completed treatment**: Patient who completed treatment but did not meet the criteria for cure or failure. **Died**: Patient who died for any reason during treatment. **Failed**: Smear-positive patient who remained smear-positive at five months or later during treatment. **Defaulted**: Patient whose treatment was interrupted for two consecutive months or more. **Transferred out:** Patient who transferred to another reporting unit and for whom the treatment outcome is not known. **Successfully treated:** Patients who were cured and those that completed treatment.

Curriculum Vitae

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